Psychiatric Medications

Practical Guide for 40 Commonly Used Psychotropics

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This work is dedicated to all who care for those who are mentally ill,

May Allah be your guardian.

This work is man-made, mistakes are possible but they are not intended.

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Introduction

Psychiatric medications have changed modern mental health care, offering hope and stability to millions of people worldwide. Yet for many clinicians, students, and patients, the field of psychopharmacology can feel overwhelming, filled with long lists of drugs, complex mechanisms, and evolving guidelines.

The aim of this book is not to add another dense textbook to the shelf, but rather to provide a clear, concise, and practical guide to psychiatric drugs and their use in everyday clinical practice.

This book is intentionally short and goal-directed. Instead of diving into theoretical details, it focuses on what truly matters: how psychiatric medications are used, why they are prescribed, and how to apply them safely and effectively. Each section is designed with the busy professional in mind, organized to allow quick access to key information, with emphasis on indications, dosage, advantages, and practical considerations.

Our goal is to bridge the gap between theory and practice. Whether you are a psychiatry trainee, a practicing clinician, or a student seeking clarity, this guide will help you navigate psychiatric drug treatment with confidence.

Above all, this book recognizes that psychiatric medications are powerful and sometimes life-saving tools, but best understood within the broader context of patient care. Used thoughtfully, they can alleviate suffering and support recovery. Used carelessly, they can cause harm or fail to reach their full potential.

By keeping the discussion grounded, focused, and clinically relevant, this book aims to support sound decision-making and better outcomes for those we serve.

Categories of Psychiatric Medications

Psychiatric medications can be grouped into broad classes based on their main therapeutic use, though many drugs have overlapping effects.

Below is a practical outline of the major categories commonly used in clinical practice:

1. **Antidepressants**

   Primarily used for depression, but also useful for anxiety disorders, obsessive–compulsive disorder (OCD), and some pain syndromes.

   Main classes:

   - **SSRIs (Selective Serotonin Reuptake Inhibitors):** e.g., fluoxetine, sertraline. First-line, relatively safe, well tolerated.
   - **SNRIs (Serotonin-Norepinephrine Reuptake Inhibitors):** e.g., Venlafaxine, Milnacipran, Duloxetine. Useful for depression with anxiety or pain.
   - **Tricyclic Antidepressants (TCAs):** e.g., amitriptyline, imipramine. Effective but more side effects and toxicity in overdose.
   - **Tetracyclic Antidepressants (TeCAs):** e.g., Mianserin.
   - **MAOIs (Monoamine Oxidase Inhibitors):** e.g., phenelzine. Reserved for resistant cases due to dietary restrictions and interactions.
   - **Serotonin Antagonist and Reuptake Inhibitor (SARI):** e.g., Trazodone.

Class	Examples	Strengths	Limitations / Cautions
SSRIs	Fluoxetine, Sertraline, Citalopram	First-line, safe in overdose, well tolerated	GI upset, sexual dysfunction, risk of discontinuation syndrome
SNRIs	Venlafaxine, Duloxetine	Useful for depression with anxiety or pain syndromes	Can increase BP, withdrawal symptoms
TCAs	Amitriptyline, Imipramine,	Effective for resistant depression, also chronic pain	Anticholinergic effects, cardiac toxicity in overdose
TeCAs	Mianserin.	depression with insomnia, anxiety, and poor appetite	rare but serious agranulocytosis, sedation, and weight gain
MAOIs	Tranylcypromine	Effective in atypical or resistant depression	Dietary restrictions, dangerous interactions (hypertensive crisis)
SARI	Trazodone	hypnotic, anxiolytic, and antidepressant properties	sedation, orthostatic hypotension, rarely priapism.

2. Antipsychotics

Used mainly for schizophrenia, bipolar disorder, severe agitation, psychosis due to other conditions.

- **Main classes:**
  - **First-Generation (Typical):** e.g., Haloperidol, Chlorpromazine. Strong dopamine blockers, higher risk of extrapyramidal side effects (EPS).
  - **Second-Generation (Atypical):** e.g., Risperidone, Olanzapine, Quetiapine. Broader mechanism, generally fewer EPS, but metabolic side effects (weight gain, diabetes).
  - **Special mention: Clozapine**, gold standard for treatment-resistant schizophrenia, but requires blood monitoring.

Class	Examples	Strengths	Limitations / Cautions
First-Generation (Typical)	Haloperidol, Chlorpromazine	Strong antipsychotic effect, rapid calming in agitation	Higher risk of extrapyramidal side effects (EPS), tardive dyskinesia
Second-Generation (Atypical)	Risperidone, Olanzapine, Quetiapine, Aripiprazole, Lurasidone	Broader efficacy, less EPS risk, some mood-stabilizing effect	Metabolic side effects (weight gain, diabetes, dyslipidemia)
Special case: Clozapine	Clozapine	Gold standard for treatment-resistant schizophrenia, reduces suicide risk	Risk of agranulocytosis, seizures; requires regular blood monitoring

3. Mood Stabilizers

Core treatment for bipolar disorder; also used in aggression, impulse control, and adjunct in depression.

- **Examples:**
    - **Lithium:** Gold standard for mania and prophylaxis; reduces suicide risk; requires regular blood level and kidney/thyroid monitoring.
    - **Valproate (Divalproex sodium):** Effective for mania and mixed states; monitor liver function and blood counts.
    - **Carbamazepine:** Useful for mania; requires blood monitoring (risk of hyponatremia, bone marrow suppression).
    - **Lamotrigine:** Effective in bipolar depression and maintenance; slow titration needed to avoid rash (Stevens-Johnson syndrome).
    - **Topiramate:** adjunctive treatment in bipolar disorder, alcohol use disorder, binge eating, obesity, PTSD, and impulsivity/aggression.

Agent	Strengths	Limitations / Cautions
Lithium	Gold standard for bipolar mania and prophylaxis, suicide risk reduction	Narrow therapeutic window, renal/thyroid monitoring essential
Valproate (Divalproex sodium)	Effective for acute mania and mixed states	Teratogenic, hepatotoxicity, weight gain, thrombocytopenia
Carbamazepine	Useful in mania, aggression	Drug interactions, hyponatremia, agranulocytosis
Lamotrigine	Best for bipolar depression and maintenance	Requires slow titration; risk of Stevens–Johnson syndrome
Topiramate	weight loss and reduction of cravings	Cognitive side effects, kidney stone risk, and lack of robust efficacy as a primary mood stabilizer.

4. Anxiolytics & Hypnotics

Used mainly for short-term relief of anxiety, insomnia, acute agitation. Best used short-term or intermittently; caution with dependence and withdrawal.

- **Examples:**
  - **Benzodiazepines:** e.g., lorazepam, diazepam. Rapid-acting, effective, but risk of dependence and sedation.
  - **Non-benzodiazepine hypnotics:** e.g., zolpidem, zopiclone. Used mainly for sleep disorders.
  - **Buspirone:** Non-sedating anxiolytic, slower onset, mainly for generalized anxiety disorder (GAD).

Class	Examples	Strengths	Limitations / Cautions
Benzodiazepines	Lorazepam, Diazepam, Clonazepam	Rapid relief of anxiety, muscle relaxant, anticonvulsant	Risk of dependence, tolerance, withdrawal, sedation
Non-benzodiazepine hypnotics ("Z-drugs")	Zolpidem, Zopiclone	Useful for insomnia, fewer hangover effects than benzodiazepines	Still habit-forming, risk of parasomnias
Buspirone	Buspirone	Non-sedating, non-addictive, safe long-term	Delayed onset (2–4 weeks), weaker efficacy

5. Stimulants and ADHD Medications

Used primarily for attention-deficit/hyperactivity disorder (ADHD), sometimes for narcolepsy.

Examples:

- **Stimulants:** e.g., Methylphenidate, Amphetamines. Improve attention and impulse control; monitor for misuse and cardiovascular risks.
- **Non-stimulants:** e.g., Atomoxetine, Modafinil, Armodafinil. Useful when stimulants are not tolerated or contraindicated.

Class	Examples	Strengths	Limitations
Stimulants	Methylphenidate, Amphetamine salts	Highly effective, rapid onset	Risk of misuse, insomnia, appetite suppression, cardiovascular risks
Non-Amphetamine stimulants	Atomoxetine, Modafinil, Armodafinil	Useful when stimulants not tolerated; non-addictive	Slower onset, less potent effect

Fluoxetine (Prozac®)

℞ ***Prozac*** *20 mg Cap.*
℞ ***Philozac*** *10 - 20 mg Cap.*
℞ ***Durazac Weekly*** *90 mg Delayed Rel. Caps.*

Pharmacology

- **Class:** SSRI (Selective Serotonin Reuptake Inhibitor).
- **Mechanism of action:** Potent and selective inhibition of serotonin transporter → ↑ extracellular serotonin in CNS.
- **Receptor profile:** Minimal affinity for muscarinic, histaminic, or adrenergic receptors → low anticholinergic and sedative effects.
- **Unique features:**
  - **Longest half-life** among SSRIs (~2–3 days; active metabolite norfluoxetine ~7–15 days).
  - Once-daily dosing; relatively **self-tapering** → lower risk of withdrawal/discontinuation syndrome compared to other SSRIs.
- **Metabolism:** Hepatic, **Strong CYP2D6 inhibitor** → high drug–drug interaction potential.

FDA-Approved Indications

1. Major Depressive Disorder (**MDD**) – adults and pediatric patients ≥8 years.
2. Obsessive–Compulsive Disorder (**OCD**) – adults and pediatric patients ≥7 years.
3. **Bulimia Nervosa** (the only SSRI with FDA approval for this indication).
4. Panic Disorder – with or without agoraphobia.
5. Premenstrual Dysphoric Disorder (PMDD).

Off-Label / Evidence-Supported Uses

- Post-traumatic stress disorder (PTSD).
- Generalized Anxiety Disorder (GAD), Social Anxiety Disorder (SAD).
- Binge Eating Disorder.
- Borderline Personality Disorder (symptom-targeted use).
- Cataplexy/narcolepsy adjunct.

Dosing Guidelines

1. **Major Depressive Disorder**
   - Initial: 20 mg once daily in the morning.
   - Range: 20–60 mg/day (some patients up to 80 mg/day).
2. **OCD**
   - Initial: 20 mg/day.
   - Effective range: 40–60 mg/day.
   - Max dose: 80 mg/day.
3. **Bulimia Nervosa**
   - Target dose: 60 mg once daily.
4. **Panic Disorder**
   - Initial: 10 mg/day × 1 week, then 20 mg/day.
   - Range: 20–60 mg/day.
5. **PMDD**
   - Continuous dosing: 20 mg daily.
   - Intermittent dosing: 20 mg daily during luteal phase only.

Special Populations

- **Hepatic impairment:** Reduce dose or extend dosing interval.
- **Children/adolescents:** Start 10–20 mg/day; usual max 60 mg/day (age-dependent).

Advantages

1. **Broad-spectrum efficacy:** Effective for depression, multiple anxiety disorders, OCD, bulimia, and PMDD.
2. **Long half-life:**
   - Lower risk of discontinuation syndrome (self-tapers).
   - Good option for patients with poor adherence.
3. **Weight neutrality / modest weight loss:** May reduce appetite; unlike mirtazapine or paroxetine, less associated with weight gain.
4. **Activating profile:** Beneficial for patients with low energy, hypersomnia, or psychomotor retardation.
5. **Pediatric approval:** One of the few SSRIs FDA-approved for depression and OCD in children/adolescents.
6. **Unique indication:** Only SSRI FDA-approved for **bulimia nervosa**.
7. **Cost-effective:** Generic widely available.

Safety and Adverse Effects

- **Common:** GI upset, insomnia, headache, tremor, anxiety/agitation (early treatment), sweating, sexual dysfunction.
- **Activation:** May worsen anxiety initially; titrate gradually.
- **Long half-life:** Delayed onset of steady state → dose adjustments should not be too rapid.
- **Serious:**
    - Serotonin syndrome (with other serotonergic drugs).
    - Hyponatremia (SIADH, elderly risk).
    - Suicidality risk in children, adolescents, and young adults (class warning).
- **Drug–drug interactions:** Strong CYP2D6 inhibitor → ↑ levels of TCAs, antipsychotics (risperidone, haloperidol), antiarrhythmics, tamoxifen (↓ efficacy).

Monitoring

- Mood, suicidality, anxiety/agitation (especially early).
- Weight, appetite, and metabolic profile.
- Sodium (elderly).
- Drug–drug interactions (esp. with CYP2D6 substrates).

Clinical Pearls

- **Morning dosing** preferred (can cause insomnia).
- **Takes longer** than some SSRIs for steady state due to long half-life.
- Best suited for **depressed patients with low energy, hypersomnia, or comorbid bulimia/OCD**.
- Avoid in patients with **significant insomnia, agitation, or weight loss** where activating effects may worsen symptoms.
- Consider switching to fluoxetine when **withdrawal syndrome is problematic with other SSRIs**.

Summary:

Fluoxetine is a **long half-life SSRI** with broad efficacy in depression, OCD, panic disorder, PMDD, and bulimia. Its **activating profile, weight neutrality, pediatric approval, and reduced withdrawal risk** are major advantages. Limitations include **CYP2D6 drug interactions, delayed onset of full effect, and potential for activation/insomnia**.

Fluvoxamine

℞ ***Faverin*** *50 - 100 mg Tab.*
℞ ***Fluxamine*** *50 - 100 mg Tab.*

Pharmacology

- **Class:** SSRI (Selective Serotonin Reuptake Inhibitor).
- **Mechanism of action:**
  - Potent inhibition of the serotonin transporter → increases extracellular serotonin levels.
  - Minimal/no activity at norepinephrine or dopamine transporters.
  - Some affinity for Sigma-1 receptors (may contribute to unique anxiolytic and anti-obsessional effects).
- **Pharmacokinetics:**
  - Half-life: ~15–20 hours (IR), ~17–26 hours (CR formulation).
  - Hepatic metabolism: (potent CYP1A2 inhibitor).
  - Significant drug–drug interaction potential (esp. with clozapine, theophylline, warfarin, caffeine).

FDA-Approved Indications

1. **Obsessive-Compulsive Disorder (OCD)** – adults and pediatric patients (≥8 years).
2. **Major Depressive Disorder (MDD)** – approved outside the US (Europe, Japan), but not FDA-approved for depression in the US.

Off-Label / Evidence-Supported Uses

- Social Anxiety Disorder (SAD).
- Panic Disorder.
- Post-Traumatic Stress Disorder (PTSD).
- Generalized Anxiety Disorder (GAD).
- Eating disorders (bulimia, binge eating).
- Trichotillomania and body dysmorphic disorder.
- Adjunct in psychotic disorders (via Sigma-1 receptor effects, some evidence).

Dosing Guidelines

A. Obsessive-Compulsive Disorder (Adults)

- **Initial:** 50 mg once daily (HS preferred to reduce nausea/somnolence).
- **Titration:** Increase by 50 mg every 4–7 days as tolerated.
- **Effective range:** 100–300 mg/day.
- **Max dose:** 300 mg/day (FDA limit).
- Often divided into BID, if dosing at >150 mg/day.

B. Pediatric OCD (≥8 years)

- **Initial:** 25 mg once daily at bedtime.
- **Titration:** Increase by 25 mg increments every 4–7 days.
- **Effective range:** 100–200 mg/day (adjust by weight and tolerability).
- **Max dose:** 200 mg/day.

C. Off-label Anxiety Disorders

- Typically start at 25–50 mg/day, titrate gradually.
- Usual range: 100–200 mg/day.

Advantages

1. **Particularly effective for OCD:**
    - Among SSRIs, Fluvoxamine has strong evidence and is often first-line in OCD.
2. **Anxiolytic profile:**
    - Sigma-1 receptor activity may enhance anti-anxiety effects beyond classic SSRI mechanism.
3. **Sedative properties (compared to activating SSRIs):**
    - Can be useful in patients with anxiety + insomnia.
4. **Pediatric efficacy:**
    - FDA-approved in children/adolescents for OCD.
5. **Lower sexual side effect burden** (some studies suggest fluvoxamine may have slightly less sexual dysfunction vs. paroxetine/sertraline, though still present).
6. **Flexible dosing:**
    - Immediate-release (IR) and controlled-release (CR) formulations available → improved tolerability and adherence.

Safety and Adverse Effects

- **Common:** Nausea, vomiting, somnolence, dizziness, headache, insomnia, sweating, dry mouth, sexual dysfunction.
- **Serious:**
    - Serotonin syndrome (esp. with other serotonergic agents).
    - Hyponatremia (SIADH, elderly risk).
    - Increased bleeding risk (with NSAIDs, anticoagulants, antiplatelets).
- **Drug–drug interactions:**
    - Potent CYP1A2 inhibitor → ↑ levels of Clozapine, Olanzapine, Theophylline, Caffeine, Warfarin.
- **Discontinuation syndrome:** May occur if stopped abruptly → taper gradually.
- **Boxed warning:** Suicidality risk in children, adolescents, young adults (class-wide for antidepressants).

Monitoring

- Mental status, suicidality.
- Side effects (GI, sedation, sexual dysfunction).
- Sodium (in elderly).
- Drug–drug interactions (esp. with Clozapine, Caffeine, Warfarin, Theophylline).
- Adherence and withdrawal symptoms upon discontinuation.

Clinical Pearls

- Best suited for **OCD and anxiety-spectrum disorders**.
- Often dosed **at night** due to sedative effects.
- **Titrate slowly** to minimize GI upset and sedation.
- Avoid with **multiple CYP1A2 substrates** (e.g., clozapine, theophylline) unless close monitoring available.

Summary:

Fluvoxamine is an **SSRI with unique sigma-1 receptor activity**, making it particularly effective for **OCD and anxiety disorders**. It is **sedating, well-suited for evening dosing**, and FDA-approved for pediatric OCD. Its main drawbacks are **drug–drug interactions (CYP1A2 inhibition)** and potential for typical SSRI adverse effects (GI upset, sexual dysfunction, withdrawal risk).

Sertraline

- ℞ ***Lustral*** *50 mg Tab*
- ℞ ***Moodapex*** *50 - 100 mg Tab*
- ℞ ***Serpass*** *100 mg Tab*

Pharmacology

- **Class:** SSRI (Selective Serotonin Reuptake Inhibitor).
- Mechanism**:** Potent inhibition of serotonin transporter (SERT) → ↑ serotonin in synaptic cleft.
- **Secondary properties:**
  - Mild dopamine transporter (DAT) inhibition (unique among SSRIs).
  - Weak sigma-1 receptor binding (possible anxiolytic/antipsychotic modulation).
- **Pharmacokinetics:**
  - Half-life: 26 hours (Norsertraline metabolite ~60–70 hours).
  - Metabolism: Hepatic (weak inhibitor of CYP2D6).
  - Protein binding: ~98%.
  - Time to steady state: ~1 week.

FDA-Approved Indications

1. Major Depressive Disorder (MDD).
2. Obsessive–Compulsive Disorder (OCD) – adults & children ≥6 years.
3. Panic Disorder.
4. Post-Traumatic Stress Disorder (PTSD).
5. Social Anxiety Disorder (SAD).
6. Premenstrual Dysphoric Disorder (PMDD).

Off-Label / Evidence-Supported Uses

- Generalized Anxiety Disorder (GAD).
- Premature ejaculation.
- Binge eating disorder.
- Body dysmorphic disorder.
- Separation anxiety disorder in children.
- Vascular depression in elderly.

Dosage and Administration

1. **Major Depressive Disorder**
    - Initial: 50 mg once daily.
    - Titration: ↑ by 25–50 mg weekly as tolerated.
    - Effective range: 50–200 mg/day.
    - **Max:** 200 mg/day.
2. **OCD**
    - Initial (adult): 50 mg/day.
    - Pediatric 6–12 years: start 25 mg/day, titrate to 50–200 mg/day.
    - Effective range: 50–200 mg/day.
3. **Panic Disorder, PTSD, SAD**
    - Initial: 25 mg/day × 1 week (to reduce activation), then ↑ to 50 mg/day.
    - Range: 50–200 mg/day.
4. **PMDD**
    - Continuous dosing: 50–150 mg daily.
    - Intermittent (luteal phase only): 50–100 mg daily during last 2 weeks of cycle.

Special Populations

- Elderly / hepatic impairment: Start low (25 mg/day), slower titration.
- Renal impairment: No adjustment required (Sertraline minimally renally excreted).

Advantages

1. **Broad spectrum of efficacy:** Strong evidence across depression, multiple anxiety disorders, PTSD, PMDD, and pediatric OCD.
2. **Well-tolerated:**
    - Lower sedation and anticholinergic burden compared to Paroxetine.
    - Less activating than Fluoxetine but not overly sedating.
3. **Intermediate half-life:**
    - Lower withdrawal risk compared to Paroxetine.
    - More forgiving of missed doses than Venlafaxine.
4. **Cardiac safety:**
    - Minimal QT prolongation (safer than Citalopram/Escitalopram in cardiac patients).
    - Commonly chosen in patients with **coronary artery disease or post-MI depression**.
5. **Pregnancy & breastfeeding:** Preferred SSRI in pregnancy and lactation (lowest risk of teratogenicity and infant exposure in breast milk).

6. **Pediatric approval:** FDA-approved for **OCD in children ≥6 years**, widely used off-label in adolescent depression/anxiety.

Safety and Adverse Effects

- **Common:** GI upset (diarrhea, nausea), headache, insomnia or somnolence, tremor, sweating, sexual dysfunction.
- **GI effects** (esp. diarrhea) are more frequent vs other SSRIs (due to mild DAT inhibition in gut).
- **Weight:** Generally, weight-neutral in short-term; mild weight gain possible long-term (less than Paroxetine or Mirtazapine).
- **Sexual dysfunction:** Comparable to other SSRIs (delayed orgasm, reduced libido).
- **Discontinuation syndrome:** Possible, but less severe than with Paroxetine or Venlafaxine.
- **Serious (rare):** Hyponatremia (SIADH, esp. elderly), serotonin syndrome, seizures (dose-dependent).

Monitoring

- Mood, suicidality, anxiety/agitation (esp. early phase).
- Weight, appetite, and sleep changes.
- Sodium in elderly or SIADH-prone patients.

Clinical Pearls

- **First-line SSRI** across depression and anxiety disorders due to efficacy, tolerability, and safety.
- **Preferred SSRI in Cardiac Patients, Pregnancy, and Breastfeeding.**
- **Start at 25 mg/day** for panic disorder/PTSD/SAD to minimize initial anxiety.
- **Diarrhea is dose-limiting** for some patients → consider bedtime dosing if activating.
- **Less likely to cause weight gain** than paroxetine, but not as neutral as fluoxetine.

Summary:

Sertraline is a **first-line SSRI** with a broad spectrum of efficacy (MDD, anxiety disorders, PTSD, PMDD, OCD including pediatric). Its **favorable safety profile, intermediate half-life, minimal cardiac risks, and suitability in pregnancy/lactation** make it one of the most versatile SSRIs in clinical practice. Limitations include **GI intolerance, sexual dysfunction, and possible discontinuation symptoms**, but overall it is among the most prescribed antidepressants worldwide.

Citalopram

- ℞ ***Citalo*** *2 mg Oral Soln.*
- ℞ ***Citalo*** *20 - 40 mg Tab*
- ℞ ***Citalofar*** *40 mg Tab*

Pharmacology

- **Class:** SSRI (Selective Serotonin Reuptake Inhibitor).
- **Mechanism:** Potent and selective inhibition of serotonin transporter (SERT) → ↑ serotonin in CNS.
- **Receptor activity:** Very low affinity for histaminic, adrenergic, or muscarinic receptors → minimal sedation and anticholinergic effects.
- **Pharmacokinetics:**
  - Half-life: ~35 hours.
  - Metabolism: Hepatic.
  - Protein binding: ~80%.
  - Metabolites: Demethylcitalopram (weak activity).

FDA-Approved Indications

- **Major Depressive Disorder (MDD)** in adults.

Off-Label / Evidence-Based Uses

- Generalized Anxiety Disorder (GAD).
- Panic Disorder.
- Obsessive–Compulsive Disorder (OCD).
- Social Anxiety Disorder.
- Premenstrual Dysphoric Disorder (PMDD).
- Post-Stroke Depression.
- Vascular depression in elderly.

Dosage and Administration

Major Depressive Disorder

- Initial: 20 mg once daily.
- Titration: May ↑ to 40 mg/day after at least 1 week.
- Usual range: 20–40 mg/day.
- Max dose: 40 mg/day (FDA restriction due to QT prolongation risk).

Special Populations

- Elderly (≥60 years): Max 20 mg/day (higher risk of QT prolongation).
- Hepatic impairment: Max 20 mg/day.
- CYP2C19 poor metabolizers or inhibitors: Max 20 mg/day.

Advantages

1. **Well-tolerated:**
    - Minimal sedation, weight gain, or anticholinergic burden.
    - Low drug–drug interaction risk compared to fluoxetine or paroxetine (weak CYP inhibition).
2. **Intermediate half-life:**
    - Lower withdrawal risk than Paroxetine; more forgiving of missed doses.
3. **Elderly use:**
    - Often used in geriatric depression (effective, generally well-tolerated).
4. **Cardiac safety at low doses:**
    - When restricted to ≤20 mg/day in elderly, still considered safe and effective.
5. **Cost-effective:**
    - Generic availability worldwide.

Limitations & Adverse Effects

- **QT prolongation (dose-dependent):**
    - 40 mg/day increases risk of Torsades de Pointes → strict FDA max-dose limits.
    - ECG monitoring recommended in high-risk patients (cardiac disease, electrolyte imbalance, concomitant QT-prolonging drugs).
- **Common side effects:** Nausea, dry mouth, sweating, tremor, insomnia or somnolence, sexual dysfunction.
- **Weight:** Generally neutral or mild gain (less than paroxetine or mirtazapine).
- **Discontinuation syndrome:** Possible, but less severe than Paroxetine/Venlafaxine.
- **Rare serious:** Hyponatremia (SIADH, especially elderly), serotonin syndrome (with other serotonergic agents).

Monitoring

- **ECG** in patients with cardiac disease, elderly, or on QT-prolonging drugs.
- Electrolytes (potassium, magnesium) in at-risk populations.
- Mood, suicidality (esp. early treatment or in <25 years).

Clinical Pearls

- **Max dose limited to 40 mg/day** (20 mg/day in elderly, hepatic impairment).
- **Safer option** when drug–drug interactions are a concern (weak CYP inhibition).
- Best suited for:
    - Patients with depression **without significant comorbid anxiety or insomnia** (sertraline or paroxetine may be better in those).
    - **Elderly or medically fragile patients** where a simple, clean SSRI is preferred.
- Avoid in:
    - Patients requiring high SSRI doses (e.g., refractory OCD, where Sertraline or Fluoxetine may be preferred).
    - Patients with **cardiac conduction abnormalities or multiple QT-prolonging meds**.

Summary:

Citalopram is a **well-tolerated SSRI** effective for depression and off-label anxiety disorders, with **low drug–drug interaction risk** and good geriatric tolerability. However, its **dose is limited by QT prolongation risk** (max 40 mg/day, 20 mg/day in elderly/hepatic impairment).

It is best considered in **depression with minimal comorbidities**, in patients where safety and tolerability are priorities, but **not the first choice for high-dose needs (OCD, severe anxiety) or in those with cardiac risk**.

Paroxetine

℞ ***Paroxetine CR*** *12.5 - 25 - 37.5 mg Tab*

℞ ***Seroxat CR*** *12.5 - 25 mg Tab*

Pharmacology

- **Class:** Selective Serotonin Reuptake Inhibitor (SSRI) → ↑ synaptic serotonin.
- **Mechanism:** Potent inhibition of serotonin transporter.
- **Additional properties:**
  - Weak norepinephrine transporter inhibition at higher doses.
  - Mild anticholinergic and antihistaminic effects (more than other SSRIs).
  - Moderate inhibition of nitric oxide synthase (may contribute to sexual side effects).
- **Pharmacokinetics:**
  - **Half-life:** Short (≈21 hours) → risk of withdrawal syndrome.
  - **Metabolism:** Hepatic (CYP2D6, paroxetine is also a strong CYP2D6 inhibitor).

FDA-Approved Indications

1. Major Depressive Disorder (MDD).
2. Obsessive–Compulsive Disorder (OCD).
3. Panic Disorder (with/without agoraphobia).
4. Social Anxiety Disorder (Social Phobia).
5. Generalized Anxiety Disorder (GAD).
6. Post-Traumatic Stress Disorder (PTSD).
7. Premenstrual Dysphoric Disorder (PMDD).

Off-Label / Evidence-Based Uses

1. Premature ejaculation (due to serotonergic delay in orgasm).
2. Migraine prophylaxis.
3. Menopausal hot flashes.
4. Bipolar depression (adjunctive, with mood stabilizer).

Dosage and Administration

A. Major Depressive Disorder

- Initial: 20 mg once daily (morning).
- Titration: Increase by 10 mg weekly if needed.

- Usual range: 20–50 mg/day.
- Max: 50 mg/day (IR); 62.5 mg/day (CR).

B. OCD

- Initial: 20 mg/day.
- Effective range: 40–60 mg/day.
- Max: 60 mg/day.

C. Panic Disorder

- Initial: 10 mg/day × 1 week, then 20 mg/day.
- Usual range: 20–40 mg/day.
- Max: 60 mg/day.

D. Social Anxiety Disorder

- Initial: 20 mg/day.
- Usual range: 20–60 mg/day.
- Max: 60 mg/day.

E. GAD

- Initial: 20 mg/day.
- Range: 20–50 mg/day.

F. PTSD

- Initial: 20 mg/day.
- Range: 20–50 mg/day.

G. PMDD

- Continuous: 12.5–25 mg CR daily.
- Intermittent (luteal phase only): 12.5–25 mg CR daily during last 2 weeks of cycle.

Advantages

1. **Broad approval for anxiety disorders:** Paroxetine has **the widest FDA-approved coverage** for anxiety spectrum (panic, GAD, SAD, PTSD, OCD).
2. **Sedating profile:** Useful in patients with depression/anxiety + insomnia, agitation, or irritability.
3. **Short half-life:** Helpful in cases where rapid discontinuation is needed (e.g., drug–drug interaction, pregnancy, adverse effect).
4. **Sexual dysfunction treatment adjunct (premature ejaculation):** Paroxetine is **most effective SSRI** for delaying ejaculation.
5. **Weight gain & sedation (when beneficial):** Can help underweight, anxious, or highly activated patients.

Limitations & Adverse Effects

- **Common:** Nausea, somnolence, fatigue, dry mouth, sweating, tremor, constipation, weight gain, sexual dysfunction.
- **Sedation & weight gain:** Greater than with Fluoxetine or Sertraline.
- **Anticholinergic effects:** Mild (blurred vision, constipation, urinary retention).
- **Withdrawal/discontinuation syndrome:**
  - **Highest risk among SSRIs** due to short half-life.
  - Symptoms: flu-like, dizziness, insomnia, anxiety, electric-shock sensations.
- **Pregnancy risk:**
  - Category D (first trimester: ↑ risk of cardiac malformations).
  - Avoid in women of childbearing age unless benefits outweigh risks.
- **Drug–drug interactions:** Strong **CYP2D6 inhibitor** → ↑ levels of TCAs, tamoxifen (↓ efficacy), some antipsychotics, beta-blockers, antiarrhythmics.

Clinical Pearls

- **Best suited for:**
  - Anxiety disorders (especially panic, GAD, PTSD, SAD).
  - Depression with insomnia or agitation.
  - Patients needing additional sedation or weight gain.
- **Avoid in:**
  - Patients with obesity/metabolic syndrome.
  - Women planning pregnancy.
  - Patients requiring minimal withdrawal risk (consider Fluoxetine instead).

Summary:

Paroxetine is a **potent SSRI** with the broadest FDA approval for anxiety disorders and proven efficacy in depression, OCD, PTSD, PMDD, and panic disorder. It is particularly useful for **anxious, agitated, or insomniac patients**, but carries risks of **weight gain, withdrawal syndrome, sexual dysfunction, and teratogenicity**. Clinical use requires careful dose titration, patient education, and monitoring of interactions due to **CYP2D6 inhibition**.

Venlafaxine

- ℞ *Idixor XR 75- 150 mg Caps.*
- ℞ *Idixor 37.5 - 75 mg Caps.*
- ℞ *Efexor XR 75- 150 mg Caps.*

Pharmacology

- **Class:** SNRI antidepressant.
- **Mechanism of action:**
  - At **low doses (<150 mg/day):** primarily inhibits serotonin reuptake (SSRI-like effect).
  - At **moderate to high doses (>150 mg/day):** inhibits both serotonin and norepinephrine reuptake.
  - At **very high doses (>300 mg/day):** weak dopamine reuptake inhibition.
- **Pharmacokinetics:**
  - Half-life: **Venlafaxine ~5 h**; **desvenlafaxine (active metabolite) ~11 h**.
  - **Metabolism:** hepatic, primarily via CYP2D6 to desvenlafaxine.
  - **Formulations:** Immediate-release (IR) and extended-release (XR)

Approved Indications

1. Major Depressive Disorder (MDD) (adults).
2. Generalized Anxiety Disorder (GAD).
3. Social Anxiety Disorder (SAD).
4. Panic Disorder.

Off-Label / Evidence-Based Uses

- Cataplexy/narcolepsy.
- Neuropathic pain, diabetic neuropathy, fibromyalgia.
- Vasomotor symptoms of menopause (hot flashes).
- ADHD, OCD, PTSD (limited evidence compared to SSRIs).

Dosing Guidelines

A. Major Depressive Disorder

- **IR:**
  - ✓ Start: 37.5 mg twice daily OR 25 mg three times daily/ Titrate every 4–7 days.
  - ✓ **Effective dose:** 150–225 mg/day in divided doses.
  - ✓ **Max dose:** 375 mg/day (inpatients).
- **XR (preferred):**
  - ✓ Start: 37.5–75 mg once daily.
  - ✓ Titrate by 75 mg at ≥4-day intervals.
  - ✓ **Effective range:** 75–225 mg/day.
  - ✓ **Max dose:** 225 mg/day (outpatients); 300–375 mg/day sometimes used in refractory cases.

B. Anxiety Disorders (GAD, SAD, Panic)

- **GAD:** Start 37.5–75 mg/day; usual dose 75–225 mg/day.
- **SAD:** Start 75 mg/day; range 75–225 mg/day.
- **Panic disorder:** Start 37.5 mg/day × 7 days, then 75 mg/day; range 75–225 mg/day.

C. Special Populations

- **Hepatic/ Renal impairment:** Reduce dose by 50%.

Advantages

1. **Broad efficacy:**
   - Effective across depression, GAD, panic, and social anxiety.
   - Some evidence of benefit in treatment-resistant depression where SSRIs fail.
2. **Dose-dependent mechanism:**
   - Functions as SSRI at low doses and as SNRI at higher doses, allowing tailored treatment.
3. Less risk of weight gain than mirtazapine or paroxetine.
4. **Pain benefits:** Off-label use in neuropathic pain and fibromyalgia due to noradrenergic effects.
5. **No significant CYP450 inhibition:**
   - Lower risk of drug–drug interactions compared to Paroxetine/Fluoxetine.

Safety Considerations

- **Common adverse effects:** nausea, headache, insomnia, sweating, dry mouth, dizziness, sexual dysfunction.
- **Dose-related hypertension:** monitor BP, especially at >150 mg/day.
- **Discontinuation syndrome:** venlafaxine has a short half-life → abrupt stop may cause dizziness, "brain zaps," irritability, flu-like symptoms. **Taper gradually.**
- **Serious risks:** serotonin syndrome, hyponatremia (SIADH), bleeding risk (with NSAIDs/anticoagulants).
- **Boxed warning:** suicidality risk in children, adolescents, young adults (class-wide).

Monitoring

- **Baseline and ongoing:**
  - Blood pressure and pulse (especially at higher doses).
  - Weight, mood, suicidality.
  - Renal and hepatic function in impaired patients.

Clinical Pearls

- **XR formulation** is preferred for adherence, smoother plasma levels, and reduced GI side effects.
- If patient is highly sensitive to side effects → start with 37.5 mg XR daily for 4–7 days.
- **Switching from SSRIs:** cross-taper may be needed to reduce serotonin syndrome risk.
- **Tapering required** when discontinuing — avoid abrupt cessation due to withdrawal.
- Consider **desvenlafaxine** (active metabolite) in poor CYP2D6 metabolizers or if venlafaxine not tolerated.

Summary:

Venlafaxine is a versatile **SNRI** effective for depression, GAD, panic, and social anxiety. Its **dose-dependent pharmacology** makes it useful across mild to severe presentations, and it offers **additional utility in pain syndromes**. Advantages include broad efficacy and relative metabolic neutrality, but clinicians must carefully monitor for **hypertension and discontinuation syndrome**.

Milnacipran

℞ ***Milnavella*** 12.5-25-50 mg Tab.

℞ ***Myodonia*** 25-50 mg Tab.

Pharmacology

Class: Serotonin–norepinephrine reuptake inhibitor (SNRI).

Mechanism of action:

Milnacipran inhibits reuptake of serotonin (5-HT) and norepinephrine (NE), increasing their synaptic availability. At low doses the serotonin effect predominates and at higher exposures NE inhibition becomes more pronounced, a property thought to underlie its analgesic activity in fibromyalgia via enhancement of descending noradrenergic pain inhibition.

Pharmacokinetics:

- Absorption / bioavailability: ~85% oral bioavailability.
- Protein binding: low (~13%).
- Half-life: racemate ~6–8 hours.
- Metabolism / elimination: primarily renal excretion (large fraction excreted unchanged); renal impairment markedly increases AUC and prolongs half-life.

Psychiatric Indications

1. **Major approved/labelled indication:**
    1. ***Fibromyalgia in adults*** (FDA-approved brand Savella in the U.S.). Although milnacipran has antidepressant activity and has been used for major depressive disorder (approved in some countries historically), its current primary marketed/label indication in several regions is fibromyalgia.
- Off-label use for depressive disorders or pain comorbid with depression occurs but depends on local approvals and guidelines.

Dosage and Administration

Typical titration for fibromyalgia (adult):

- Day 1: 12.5 mg once.
- Days 2–3: 12.5 mg twice daily.
- Days 4–7: 25 mg twice daily.
- Thereafter: target **50 mg twice daily (100 mg/day)**.

Administration notes:

- Oral, with or without food (taking with food may reduce GI upset).
- For **renal impairment** dose adjustments are required.

Discontinuation:

- Taper gradually when stopping to reduce risk of discontinuation symptoms (dizziness, irritability, sensory disturbances).

Advantages

- **Analgesic benefit in fibromyalgia:** demonstrated reductions in pain and improvements in patient global impression, fatigue and function.
- **Dual 5-HT/NE action**: useful where both mood and pain modulation are targeted; the NE component is thought to contribute to analgesic effect.
- **Lower anticholinergic burden than TCAs** (fewer anticholinergic adverse effects such as severe constipation or marked sedation).
- **Flexible titration** that allows early low dosing to improve tolerability (GI and cardiovascular side effects often dose-related).

Adverse Effects & Limitations

- **Common:** nausea, headache, constipation, dizziness, insomnia, increased heart rate, palpitations, sweating, hypertension, dry mouth. Nausea is the most frequently reported early adverse event.
- **Serious risks / limitations:**
  - **Increases in blood pressure and heart rate.**
  - **Suicidality risk:** as with other antidepressants.
  - **Renal elimination limits use in renal impairment:** dose adjustment required; severe impairment substantially increases exposure and elimination half-life.
  - **Withdrawal / discontinuation effects** if abruptly stopped.

Monitoring

- **Blood pressure and heart rate:** baseline and periodically during treatment, more frequently after dose escalation or in patients with cardiovascular risk.
- **Renal function:** baseline creatinine / eGFR and repeat as clinically indicated
- **Pregnancy / lactation considerations:** not routinely recommended as first-line in pregnancy without specialist guidance.

Clinical Pearls

- **Start very low and titrate** slowly during the first week to improve tolerability - nausea and dizziness are common early but often diminish.
- **Target dose for fibromyalgia** is typically 50 mg twice daily (100 mg/day); many patients achieve clinically meaningful improvement at this dose. Consider patient response before escalating above 100 mg/day.
- **Check renal function** before initiation, because ~50–60% of the dose can be excreted unchanged, impaired renal function increases exposure; do not rely on standard dosing in renal impairment.
- **If combining with other serotonergic drugs** (e.g., SSRIs), be vigilant for serotonin syndrome and consider washout periods if changing classes.
- **Cardiovascular caution:** because milnacipran can raise BP and heart rate, avoid or use caution in patients with uncontrolled hypertension or significant cardiac disease.

Summary

Milnacipran is an SNRI with clinically useful dual 5-HT and NE reuptake inhibition. Its primary contemporary clinical role is **management of fibromyalgia in adults**, where it reduces pain and improves function and fatigue. The typical regimen titrates during week 1 to **50 mg twice daily (100 mg/day)**; renal impairment requires dose adjustment because elimination is largely renal.

Advantages include demonstrated analgesic benefit in fibromyalgia and fewer anticholinergic effects than older agents; limitations include GI side effects, tachycardia/hypertension risk, suicidality warning, and pronounced dependence on renal clearance. Monitor **BP/HR**, **renal function**, and **mood/suicidality**, and taper when stopping.

Duloxetine (Cymbalta®)

℞ *Cymbatex 20- 30 - 60 mg Caps.*

℞ *Cymbalta 30 - 60 mg Caps.*

Pharmacology

- **Class:** Serotonin–norepinephrine reuptake inhibitor (SNRI).
- **Mechanism of action:**
  - Potent inhibitor of serotonin (5-HT) and norepinephrine (NE) transporters.
  - Mild dopamine reuptake inhibition in prefrontal cortex (clinically relevant to mood and cognition).
- **Receptor profile:** Negligible affinity for histamine H_1, muscarinic, or adrenergic receptors → lower sedation and anticholinergic effects than tricyclics.
- **Half-life:** ~12 hours (once or twice daily dosing).
- **Metabolism:** Extensive hepatic metabolism via CYP1A2 and CYP2D6 → avoid in substantial liver impairment or heavy alcohol use.

FDA-Approved Indications

1. Major Depressive Disorder (MDD) – adults.
2. Generalized Anxiety Disorder (GAD) – adults and children ≥7 years.
3. Diabetic Peripheral Neuropathic Pain.
4. Fibromyalgia.
5. Chronic musculoskeletal pain (e.g., chronic low back pain, osteoarthritis pain).

Off-Label / Evidence-Supported Uses

- Stress urinary incontinence (approved in EU, not US).
- Chemotherapy-induced peripheral neuropathy.
- Painful polyneuropathies (non-diabetic).

Dosing Guidelines

A. Major Depressive Disorder

- **Initial:** 30–60 mg once daily.
- **Target/Effective range:** 60–120 mg/day (once or divided BID).
- **Max:** 120 mg/day

B. Generalized Anxiety Disorder

- **Start:** 30 mg once daily × 1 week, then increase to 60–120 mg/day.

C. Neuropathic Pain (diabetic, fibromyalgia, musculoskeletal pain)

- **Start:** 30 mg once daily × 1 week, then 60 mg daily.
- **Effective dose:** 60 mg daily.
- **Max:** 120 mg/day (may be used in refractory cases, but increased side effects).

D. Special Populations

- **Renal impairment:** Avoid if GFR <30 mL/min.
- **Hepatic impairment:** Contraindicated in chronic liver disease, cirrhosis, or substantial alcohol use.
- **Elderly:** Start lower (30 mg/day) and titrate cautiously.

Advantages

1. **Dual efficacy:**
    - Treats both **psychiatric symptoms** (depression, anxiety) and **somatic/pain syndromes** (fibromyalgia, neuropathic pain, musculoskeletal pain).
2. **Less sedating / fewer anticholinergic effects** than tricyclics.
3. **Weight neutral to modest weight loss** in some patients (advantage over Mirtazapine, Paroxetine, Olanzapine).
4. **Improves functional outcomes:** Evidence supports benefits on quality of life, physical functioning, and return to work in chronic pain patients.
5. **Low risk of drug–drug interactions compared to venlafaxine:**
    - Duloxetine moderately inhibits CYP2D6 (care with tricyclics, tamoxifen, some antipsychotics), but overall safer with polypharmacy than many alternatives.

Safety and Adverse Effects

- **Common:** Nausea, dry mouth, constipation, decreased appetite, fatigue, sweating, insomnia.
- **Serious:**
    - **Hepatotoxicity** (contraindicated in liver disease or heavy alcohol use).
    - **Hypertension** (dose-related).
    - **Serotonin syndrome** (with serotonergic agents).
    - **Withdrawal/discontinuation syndrome** (dizziness, "brain zaps," irritability → taper slowly).

Monitoring

- Baseline and periodic:
    - Blood pressure.
    - Liver function tests (esp. if risk factors present).
    - Mood and suicidality.
- Monitor for adherence and withdrawal symptoms on discontinuation.

Clinical Pearls

- **Start low, titrate slow** to minimize nausea (common early side effect).
- Best suited for **patients with both depression/anxiety and comorbid pain syndromes**.
- Unlike venlafaxine, duloxetine can be given **once daily** at therapeutic doses.
- Avoid in **significant liver impairment or alcohol abuse**.
- XR capsule may be opened and sprinkled on applesauce for patients with swallowing difficulty (must not be crushed/chewed).

Summary:

Duloxetine is a versatile **SNRI** with efficacy in **depression, anxiety, and chronic pain conditions**, offering both mood and somatic symptom relief. It is generally weight-neutral, less sedating than tricyclics, and well-suited for patients with comorbid pain syndromes. Limitations include **hepatotoxicity risk** and need for gradual discontinuation.

Its absorption is delayed by food, food delays time of reaching max. concentration.

Reboxetine

℞ ***Senorein*** 4 mg Tab.

Pharmacology

- **Class:** Selective Norepinephrine Reuptake Inhibitor (NRI).
- **Mechanism of Action:**
  - Potently and selectively inhibits the **norepinephrine transporter (NET)** → ↑ synaptic NE.
  - Minimal activity on serotonin or dopamine transporters.
  - Negligible affinity for muscarinic, histamine, or adrenergic receptors → fewer anticholinergic and sedative effects compared to TCAs.
- **Pharmacokinetics:**
  - Metabolism: Hepatic, mainly via CYP3A4.
  - Half-life: ~13 hours.
  - Excretion: Urine (mostly metabolites, ~10% unchanged).

Psychiatric Indications

Approved

- **Major Depressive Disorder (MDD):**
  - Indicated for acute and maintenance treatment of depression (EMA approval, but **not FDA-approved in the U.S.**).
  - Particularly beneficial for patients with **psychomotor retardation, low energy, or hypersomnia**.

Off-label / Investigational

- Attention-Deficit/Hyperactivity Disorder (ADHD): Some evidence of benefit in adults.
- Panic disorder and social anxiety disorder: Mixed evidence.
- Narcolepsy / hypersomnia syndromes: Studied for alertness-promoting effects.
- Fatigue in neurological or medical conditions (e.g., MS, cancer-related fatigue).

Dosage and Administration

- **Adults (MDD):**
  - Initial: 4 mg **BID** (total 8 mg/day).
  - May titrate to **10–12 mg/day** after 3 weeks based on response and tolerability.
  - Maximum: 12 mg/day.
- **Elderly / renal or hepatic impairment:** Start lower (2–4 mg BID), max 6 mg/day.
- **Onset of effect:** Often within 2–4 weeks.

Advantages

1. Activating profile → useful in depression with fatigue, anergia, poor concentration, hypersomnia.
2. Low risk of sexual dysfunction compared to SSRIs/SNRIs.
3. Minimal weight gain (weight-neutral or slight weight loss in some).
4. No sedative or anticholinergic burden → safer in elderly than TCAs.
5. Not associated with serotonin syndrome (can be combined with SSRIs in some resistant cases).
6. Safer cardiovascular profile than TCAs (does not block sodium channels).

Adverse Effects & Limitations

- **Common:** Dry mouth, constipation, urinary hesitancy/retention, sweating, tachycardia, insomnia.
- **Cardiovascular:** Orthostatic hypotension, tachyarrhythmia (rare).
- **Neuropsychiatric:** Agitation, anxiety, insomnia, irritability.
- **Contraindications:**
    - Seizure disorders.
    - Narrow-angle glaucoma.
    - Urinary retention or severe prostatic hypertrophy.
    - Concomitant MAOI use (risk of hypertensive crisis).

⚠ **Evidence limitations:**

- Meta-analyses (e.g., Cipriani et al., *Lancet Psychiatry*, 2018) suggest **inferior efficacy compared to SSRIs/SNRIs** in MDD.
- Consequently, Reboxetine is considered a **second-line antidepressant** in most guidelines.

Monitoring

- **Baseline:** BP, heart rate, urologic history.
- **Ongoing:** Monitor for insomnia, agitation, urinary retention, suicidality (especially early treatment).
- No routine serum drug monitoring required.

Clinical Pearls

- Best for **patients with depression + fatigue/low energy**, where SSRIs cause sedation, weight gain, or sexual side effects.
- Avoid in **patients with anxiety-predominant depression**, as it may worsen agitation/insomnia.
- May be considered when SSRIs/SNRIs are poorly tolerated or contraindicated.
- Combination strategy: sometimes added to SSRIs to target **residual anergia and low motivation**.

Summary

Reboxetine is a **selective norepinephrine reuptake inhibitor** approved for depression in Europe but not in the U.S. It is **activating, weight-neutral, and has fewer sexual side effects** compared to SSRIs, making it useful in patients with **low-energy depression**. However, large-scale evidence suggests it is **less effective overall than SSRIs/SNRIs**, so it is usually reserved for **second-line use** or for patients who cannot tolerate serotonergic antidepressants.

Clomipramine

℞ ***Anafronil SR*** *75 mg Tab*

℞ ***Anafronil*** *25 mg Tab*

Pharmacology

- **Class:** Tricyclic antidepressant (TCA).
- **Mechanism of action:**
  - **Potent serotonin reuptake inhibition** (the most serotonergic of TCAs).
  - Moderate norepinephrine reuptake inhibition.
  - Antagonist at **histaminic (H1), muscarinic (M1), and α1-adrenergic** receptors → sedation, anticholinergic, and cardiovascular side effects.
- **Metabolism:**
  - Hepatic via CYP2D6.
  - Active metabolite: **desmethylclomipramine** (greater norepinephrine reuptake inhibition).
- **Half-life:** 19–37 hours (metabolite ~54–77 hours).

FDA-Approved Indications

- **Obsessive–Compulsive Disorder (OCD)** (adults and children ≥10 years).

Off-Label / Evidence-Supported Uses

- Major Depressive Disorder (MDD), especially with melancholic or treatment-resistant features.
- Panic Disorder, Agoraphobia.
- Chronic pain syndromes (neuropathic pain, fibromyalgia).
- Cataplexy/narcolepsy.
- Body Dysmorphic Disorder (BDD).
- Premature ejaculation (off-label, due to serotonergic effect).

Dosage and Administration

A. Obsessive–Compulsive Disorder (Adults)

- Initial: 25 mg/day (bedtime or divided).
- Titration: ↑ gradually by 25 mg every 4–7 days.
- Therapeutic range: 100–250 mg/day (usually divided doses).
- Maximum: 250 mg/day.
- Onset: OCD improvement may take 6–12 weeks.

B. Pediatric OCD (≥10 years)

- Initial: 25 mg/day.
- Titration: Gradually ↑ to 3 mg/kg/day or 100–200 mg/day (whichever lower).

C. Depression (off-label)

- 100–200 mg/day (divided).

Administration tips

- Give larger portion of dose at bedtime (to reduce daytime sedation).
- Plasma level monitoring recommended in high doses or toxicity suspicion.

Advantages

1. **Gold-standard TCA for OCD:**
    - Historically the most effective TCA for obsessive–compulsive symptoms (often as effective as or more effective than SSRIs).
    - Still used when patients fail ≥2 SSRIs.
2. **Broad efficacy:**
    - Useful in treatment-resistant depression, anxiety disorders, pain syndromes.
3. **Dual mechanism (serotonin + norepinephrine):**
    - More robust response in melancholic or severe depression compared to SSRIs alone.
4. **Alternative for non-responders to SSRIs:**
    - Especially valuable in **refractory OCD**.
5. **Long clinical track record:**
    - Decades of data on efficacy in OCD and depression.

Limitations & Adverse Effects

- **Anticholinergic:** Dry mouth, constipation, blurred vision, urinary retention.
- **Antihistaminic:** Sedation, weight gain.
- **Antiadrenergic:** Orthostatic hypotension, dizziness.
- **Cardiac:** QT prolongation, tachycardia, conduction block, arrhythmias → baseline ECG recommended (esp. >40 years or cardiac history).
- **CNS:** Tremor, seizures (dose-dependent risk ↑ at >250 mg/day).
- **Sexual dysfunction:** Decreased libido, anorgasmia.
- **Overdose risk:** Like other TCAs, overdose can be fatal (arrhythmias, seizures, CNS depression).
- **Withdrawal symptoms:** Insomnia, flu-like symptoms, rebound anxiety if abruptly discontinued.

Monitoring

- **Baseline and follow-up ECG** (especially in elderly or cardiac disease).
- **Blood pressure, HR** (orthostasis, tachycardia).
- **Weight and BMI.**
- **Electrolytes (Na+):** SIADH risk.
- **Therapeutic drug monitoring**: target plasma concentration 150–250 ng/mL (clomipramine + desmethylclomipramine).

Clinical Pearls

- **Best for:**
  - Severe or refractory OCD.
  - Depression with strong serotonergic symptoms (rumination, obsessionality).
  - Patients not responding to SSRIs.
- **Avoid in:**
  - Cardiac disease, epilepsy, glaucoma, prostatic hypertrophy, elderly sensitive to anticholinergics.
  - Patients at suicide risk (overdose danger).
- **Switching strategy:**
  - When moving from SSRIs (esp. fluoxetine), allow washout due to drug–drug interactions.
  - Monitor for **serotonin syndrome** if combined with SSRIs, MAOIs, or other serotonergic drugs.

Summary:

Clomipramine is a **serotonergic TCA** and remains a **benchmark treatment for OCD**, especially in **refractory cases** where multiple SSRIs have failed.

It also has strong efficacy in depression, anxiety, and certain pain syndromes.

However, its use is limited by **anticholinergic, sedative, cardiovascular, and seizure risks**, as well as high lethality in overdose.

Careful patient selection, slow titration, and close monitoring (including ECG) are essential.

Amitriptyline

℞ ***Tryptizol*** *10 mg Tab*

℞ ***Tryptizol*** *25 mg Tab*

Pharmacology

- **Class:** Tricyclic antidepressant (TCA).
- **Mechanism of Action:**
  - Inhibits **serotonin (5-HT) and norepinephrine (NE) reuptake** → ↑ synaptic concentrations.
  - **Receptor antagonism:**
    - **Histamine H1** → sedation, weight gain.
    - **Muscarinic M1** → anticholinergic side effects.
    - **Alpha-1 adrenergic** → orthostatic hypotension.
  - Weak sodium channel blockade → analgesic effects in neuropathic pain.
- **Metabolism:** Hepatic via CYP2D6 → active metabolite **nortriptyline** (less sedating, more noradrenergic).
- **Half-life:** 10–28 hours.

FDA-Approved Indications

- **Major Depressive Disorder (MDD)** (particularly endogenous/melancholic depression).

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3. Off-Label / Evidence-Supported Uses

- Chronic neuropathic pain (diabetic neuropathy, postherpetic neuralgia).
- Migraine prophylaxis.
- Tension-type headache.
- Fibromyalgia.
- Irritable bowel syndrome (IBS), functional GI disorders.
- Insomnia (due to sedating properties).
- Anxiety disorders, panic disorder, PTSD (less common today due to SSRIs/SNRIs preference).
- Nocturnal enuresis in children (second-line, after behavioral therapy and desmopressin).

Dosage and Administration

A. Major Depression (Adults)

- Initial: 25–50 mg/day, usually at bedtime.
- Titration: Increase by 25–50 mg every 3–7 days.

- Therapeutic range: 100–300 mg/day (given in divided doses or single bedtime dose).
- Maximum: 300 mg/day.
- Onset: 2–4 weeks for mood improvement.

B. Neuropathic Pain / Migraine Prophylaxis

- Initial: 10–25 mg at bedtime.
- Titration: Increase by 10–25 mg every 1–2 weeks.
- Typical effective dose: 25–75 mg/day.
- Maximum (for pain): ~100 mg/day (higher rarely tolerated due to side effects).

C. Pediatric Enuresis (≥6 years)

- Initial: 10–20 mg at bedtime.
- May titrate up to: 25–50 mg at bedtime (max 2.5 mg/kg/day).
- Duration: Reassess after 1–3 months.

Advantages

1. **Broad-spectrum efficacy:** Works not only for depression but also for **pain syndromes, headaches, insomnia, and GI disorders.**
2. **Sedative properties:** Useful for patients with depression and comorbid **insomnia or agitation.**
3. **Analgesic effect independent of mood:** Beneficial for chronic pain even in non-depressed patients.
4. **Migraine prophylaxis:** Long-standing efficacy with strong clinical evidence.
5. **Cost-effective:** Inexpensive generic widely available worldwide.
6. **Active metabolite (nortriptyline):** Allows alternative if amitriptyline not tolerated.

Limitations & Adverse Effects

- **Anticholinergic:** Dry mouth, blurred vision, constipation, urinary retention, cognitive impairment (especially in elderly).
- **Antihistaminic (H1):** Sedation, weight gain, increased appetite.
- **Antiadrenergic (α1):** Orthostatic hypotension, dizziness, reflex tachycardia.
- **Cardiac:** QT prolongation, conduction block, arrhythmias → avoid in patients with recent MI, arrhythmias, or prolonged QTc.
- **CNS:** Confusion, delirium (especially elderly), tremor, lowered seizure threshold.
- **Sexual dysfunction:** Decreased libido, anorgasmia, erectile dysfunction.
- **Overdose risk:** Very dangerous (arrhythmias, seizures, CNS depression) – requires caution in suicidal patients.

Monitoring

- **Baseline ECG** in patients >40 years or with cardiac history.
- **Blood pressure and HR.**
- **Weight, BMI, metabolic profile.**
- **Electrolytes (Na^+):** risk of hyponatremia/SIADH.
- **Therapeutic plasma level (optional):** 80–200 ng/mL (combined amitriptyline + nortriptyline).

Clinical Pearls

- Start **low and go slow**, especially in elderly (initial dose 10 mg at bedtime).
- Use **bedtime dosing** to maximize sedation and reduce daytime drowsiness.
- Avoid in patients with **angle-closure glaucoma, urinary retention, epilepsy, cardiac conduction disease.**
- For pain and migraine → much lower doses than in depression are usually effective.
- Switching strategy: If changing from SSRI (esp. fluoxetine due to long half-life), allow adequate washout to avoid interactions.

Summary:

Amitriptyline is a **prototypical tricyclic antidepressant** with strong efficacy in **major depression**, but nowadays is more often used at **low doses for neuropathic pain, migraine prophylaxis, fibromyalgia, and insomnia** due to its sedative and analgesic effects. Despite its broad utility, its use is limited by **anticholinergic, cardiovascular, and overdose risks**. Careful patient selection and slow titration are essential.

Mianserin

℞ ***Tolvon*** 30 mg Tab.

Pharmacology

- **Class:** Tetracyclic antidepressant (TeCA).
- **Mechanism of Action:**
  - **α2-adrenergic antagonist** → enhances release of norepinephrine and serotonin.
  - **5-HT2A/5-HT2C and 5-HT3 antagonist** → improves sleep, reduces anxiety, and lowers risk of sexual side effects.
  - **Histamine H1 antagonist** → sedative and hypnotic effects.
- **Pharmacokinetics:**
  - Oral bioavailability: ~20–30%.
  - Half-life: ~21–61 hours (allows once-daily dosing).
  - Metabolism: Hepatic (CYP-mediated).
  - Excretion: Mainly renal (metabolites).

Psychiatric Indications

Approved (Europe, Australia, Japan)

- **Major depressive disorder (MDD)** – especially when insomnia or anxiety are present.

Off-label / Clinical Use

- Depressive disorders in the elderly (better tolerability than tricyclic antidepressants).
- Insomnia (low doses for sleep induction).
- Anxiety disorders (GAD, panic disorder, adjunct use).
- Cancer and palliative care – appetite stimulation, sleep improvement.

*Note: Not FDA-approved in the U.S.; largely replaced by **Mirtazapine**, a close analogue with similar pharmacology but broader clinical adoption.*

Dosage and Administration

- **Adults (MDD):**
  - Start: **15 mg PO at night** (due to sedation).
  - Titrate gradually every 1–2 weeks.
  - Usual range: **30–45 mg/day**.
  - Maximum: **60 mg/day**.
- **Elderly:** Start lower (10–20 mg) with slower titration.

Advantages

1. **Improves sleep** → strong sedative effect beneficial in depression with insomnia.
2. **Low risk of sexual dysfunction** compared to SSRIs/SNRIs.
3. **Low risk of anticholinergic side effects** vs. tricyclics (safer in elderly).
4. **Minimal cardiotoxicity** relative to TCAs.
5. **Useful in the elderly** → less orthostatic hypotension than TCAs, though caution still required.
6. **Potential anxiolytic and appetite-stimulating properties**.

Adverse Effects & Limitations

- **Common:** Sedation, weight gain, increased appetite, dry mouth, dizziness, constipation.
- **Serious:**
    - **Agranulocytosis (rare, ~1/10,000 patients)** → monitor CBC if infection symptoms develop.
    - Orthostatic hypotension (α1-blockade).
    - Hepatic enzyme elevation.
- **Overdose:** Less cardiotoxic than TCAs, but may cause sedation, hypotension, seizures.
- **Contraindications:**
    - Acute liver disease.
    - Recent myocardial infarction.
    - Known blood dyscrasias.

Monitoring

- **Baseline and periodic CBC** (for risk of agranulocytosis).
- **Liver function tests** if clinically indicated.
- **Weight and metabolic monitoring** due to appetite/weight gain.
- **Elderly:** Monitor orthostatic BP.

Clinical Pearls

- **Low-dose use (10–30 mg):** Mainly sedative/hypnotic.
- **Higher doses (30–60 mg):** More antidepressant effect, relatively less sedation.
- **Augmentation:** Sometimes combined with SSRIs/SNRIs for resistant depression (though mirtazapine is more common for this strategy).
- **Replacement by Mirtazapine:** Mirtazapine shares the same mechanism (NaSSA = noradrenergic and specific serotonergic antidepressant), but has fewer hematological risks, making it the **preferred agent** in most regions today.

Summary

Mianserin is a **tetracyclic antidepressant** that works by **α2-adrenergic and serotonergic receptor antagonism**. It is especially helpful in **depression with insomnia, anxiety, and poor appetite**, and has **advantages** over tricyclics such as fewer anticholinergic and cardiovascular side effects. However, its use is limited by **rare but serious agranulocytosis**, sedation, and weight gain.

In modern practice, **Mirtazapine** has largely replaced Mianserin, but it remains a valuable agent in certain populations (elderly, insomnia-prone, or SSRI-intolerant patients).

Tranylcypromine

℞ ***Parnetil*** 10 mg Tab.

Pharmacology

- **Class:** Irreversible, non-selective monoamine oxidase inhibitor (**MAOI**); structurally related to amphetamine.
- **Mechanism of Action:**
  - **Irreversibly inhibits both MAO-A and MAO-B** → increases synaptic serotonin (5-HT), norepinephrine (NE), and dopamine (DA).
  - Amphetamine-like structure may contribute to **mild stimulant effect**.
- **Pharmacokinetics:**
  - Oral bioavailability: ~50%.
  - Onset: Antidepressant effects typically after 2–3 weeks.
  - Half-life: ~1.5–3 h, but effects last **days to weeks** due to irreversible enzyme inhibition.
  - Metabolism: Hepatic (acetylation, conjugation).
  - Excretion: Renal.

Psychiatric Indications

Approved

- **Major Depressive Disorder (MDD)** – particularly in **treatment-resistant depression** (TRD).
- **Atypical depression** – hypersomnia, hyperphagia, leaden paralysis, rejection sensitivity.

Off-label / Clinical Use

- Bipolar depression (with mood stabilizer co-treatment).
- Social anxiety disorder (historical evidence).
- Panic disorder (less common now due to safer alternatives).
- Parkinson's disease (rare, adjunctive to dopaminergic therapy).

Dosage and Administration

- **Adults (MDD):**
  - Start: 10 mg PO **BID**.
  - Increase every 1–3 weeks by 10 mg/day as tolerated.
  - Typical effective dose: **30–60 mg/day** in divided doses.
  - Maximum: 60 mg/day (some refractory cases up to 80 mg/day).
- **Elderly:** Start lower (10 mg/day) due to cardiovascular risks.

Advantages

1. **Highly effective in treatment-resistant depression** → can benefit patients who fail SSRIs, SNRIs, TCAs, and atypical antidepressants.
2. **Particularly useful in atypical depression** with hypersomnia, hyperphagia, and leaden paralysis.
3. **May improve motivation and energy** due to mild stimulant-like properties.
4. **Low risk of sexual dysfunction and weight gain** compared to SSRIs/SNRIs.
5. **May benefit anergic or dopamine-deficit syndromes** (amotivation, apathy).
6. **Different mechanism** → valuable in patients not responding to serotonergic agents.

Adverse Effects & Limitations

- **Common:** Insomnia, agitation, dizziness, orthostatic hypotension, headache, dry mouth, constipation.
- **Hypertensive crisis:** Risk with **tyramine-rich foods** ("cheese reaction") or sympathomimetic drugs.
- **Serotonin syndrome:** Risk if combined with SSRIs, SNRIs, TCAs, other serotonergic drugs.
- **Cardiovascular:** Hypertension, arrhythmias; caution in elderly and cardiac disease.
- **Hepatotoxicity:** Rare, but monitor LFTs in long-term use.
- **Overdose risk:** CNS stimulation → convulsions, hyperthermia, cardiovascular collapse.
- **Contraindications:**
    - Concomitant serotonergic or adrenergic agents (SSRIs, SNRIs, TCAs, meperidine, tramadol, decongestants).
    - Pheochromocytoma, uncontrolled hypertension, cardiovascular disease.
    - Cerebrovascular disease.

Monitoring

- **Baseline:** BP, cardiovascular history, liver function tests.
- BP monitoring (risk of orthostatic hypotension or hypertensive crisis).
- Mental status for mood switches or suicidality.
- Drug–drug and food interaction vigilance.

Clinical Pearls

- **Dietary restrictions:** Avoid **tyramine-rich foods** (aged cheeses, cured meats, soy, draft beer) to prevent hypertensive crisis.
- **Washout periods:**
    - 2 weeks after stopping tranylcypromine before starting serotonergic drugs.
    - 5 weeks after fluoxetine before starting tranylcypromine (due to long half-life).

- **Best candidates:**
    - Patients with **treatment-resistant, atypical, or anergic depression**.
    - Patients with **severe melancholic or suicidal depression** where other agents failed.
- **Combination therapy:** Can be combined with mood stabilizers (e.g., lithium, lamotrigine) in bipolar depression.

Summary

Tranylcypromine is a **non-selective, irreversible MAOI** with unique efficacy in **treatment-resistant and atypical depression**.

Its **advantages** include effectiveness where other antidepressants fail, energizing properties, and lower risk of sexual dysfunction.

Its **limitations** are significant: dietary restrictions, serious drug interactions, risk of hypertensive crisis, and cardiovascular side effects. As such, it is reserved for **specialist use in resistant cases** under strict monitoring.

Trazodone

℞ ***Trittico*** 50- 100 mg Tab.

Pharmacology

- **Class:** Serotonin Antagonist and Reuptake Inhibitor (SARI); phenylpiperazine derivative.
- **Mechanism of Action:**
  - **Antagonist at 5-HT_2A and 5-HT_2C receptors** → anxiolytic, antidepressant, and sleep-promoting effects.
  - **Weak serotonin reuptake inhibition.**
  - **α_1-adrenergic receptor antagonism** → orthostatic hypotension, sedation.
  - **Histamine H_1 receptor antagonism** → strong sedative/hypnotic effect.
- **Pharmacokinetics:**
  - Half-life: 6–11 h (short, often requires divided doses for antidepressant effect).
  - Metabolism: Hepatic (CYP3A4 → active metabolite mCPP [m-chlorophenylpiperazine], which may contribute to anxiogenic effects).
  - Excretion: Renal and biliary.

Psychiatric Indications

Approved Uses

- **Major Depressive Disorder (MDD):** Effective at antidepressant doses (≥150 mg/day).

Off-label / Common Clinical Uses

- Insomnia: At low doses (25–100 mg before sleep) as hypnotic (most frequent current use).
- Anxiety disorders: Generalized anxiety disorder (GAD), PTSD, panic disorder (limited evidence).
- Agitation in dementia / delirium: Low-dose trazodone sometimes used in elderly.
- Adjunct for antidepressant-induced insomnia or sexual dysfunction (though evidence is mixed).

Dosage and Administration

- **Depression (adult):**
  - Initial: 150 mg/day (divided BID/TID or XR once daily).
  - Titration: Increase by 50 mg/day every 3–4 days as tolerated.
  - Typical therapeutic range: **150–400 mg/day** (up to 600 mg/day in inpatients).
- **Insomnia (off-label):**
  - 25–100 mg (usually single dose).
- **Elderly / hepatic impairment:** Start low (25–50 mg), titrate slowly.

⚠ **Important distinction:**

- **Low doses (25–100 mg HS):** Hypnotic effect (via H_1 and α_1 blockade).
- **High doses (150–400 mg):** Antidepressant effect (via 5-HT_2 antagonism + SERT inhibition).

Advantages

1. **Dual utility:** Antidepressant at higher doses, hypnotic at lower doses.
2. **Beneficial in depression with insomnia, agitation, or anxiety.**
3. **Safe in overdose compared to TCAs** (less cardiotoxic).
4. **Non-addictive hypnotic alternative** (unlike benzodiazepines, Z-drugs).
5. **Sexual side effects less prominent** than SSRIs at low doses (may even mitigate SSRI-induced sexual dysfunction in some patients).
6. **Useful in elderly for agitation and sleep disturbance** when cautious dosing is applied.

5Adverse Effects & Limitations

- **Common:** Sedation, dizziness, dry mouth, blurred vision, headache, nausea, constipation.
- **Orthostatic hypotension:** Due to α_1 blockade → caution in elderly, fall risk.
- **Priapism (rare but serious):** ~1/6000 incidence; urologic emergency.
- **Cognitive dulling / daytime sedation:** Especially with hypnotic doses.
- **Arrhythmias / QT prolongation:** Risk ↑ with overdose or drug interactions.
- **mCPP metabolite:** May cause anxiety or agitation in some.
- **Drug interactions:** CYP3A4 inhibitors (ketoconazole, erythromycin) ↑ levels; caution with serotonergic agents (risk of serotonin syndrome).

Monitoring

- **Baseline:** BP, cardiac history, ECG (if cardiac risk).
- **Follow-up:** Monitor for orthostatic hypotension, sedation, suicidality (esp. early in depression treatment).
- **In elderly:** Fall risk assessment.

Clinical Pearls

- **Insomnia:** One of the most widely prescribed off-label hypnotics in psychiatry.
- **Best fit:** Patients with **MDD + insomnia/anxiety** who cannot tolerate SSRIs/SNRIs.
- **Elderly:** Often used in low doses for sleep, but risk of falls and hyponatremia should be weighed.
- **Not first-line for depression** due to sedation and BID/TID dosing needs (unless XR used).
- **Safer in overdose** compared with TCAs, but arrhythmias possible at toxic levels.

Summary

Trazodone is a **serotonin antagonist and reuptake inhibitor (SARI)** with dual clinical profiles: **low-dose sedative** (25–100 mg HS for insomnia) and **high-dose antidepressant** (150–400 mg/day for MDD). It is valued for its **hypnotic, anxiolytic, and antidepressant properties**, particularly in patients with **depression and comorbid insomnia**. Its advantages include **safety in overdose, low abuse potential, and utility in elderly agitation**, but its use is limited by **sedation, orthostatic hypotension, and rare priapism**.

Vortioxetine

℞ ***Depratiox*** *10-15-20 mg tab*
℞ ***Brintellix*** *10-20 mg tab*

Pharmacological Profile

- **Class:** Multimodal antidepressant (serotonin modulator and stimulator).
- **Mechanism of action:**
  - **Serotonin transporter inhibition** → SSRI effect.
  - **5-HT$_1$A receptor agonist** (enhances serotonergic neurotransmission).
  - **5-HT$_3$ and 5-HT$_7$ receptor antagonism** and **5-HT$_1$B partial agonism** → thought to modulate glutamate, dopamine, norepinephrine, histamine, and acetylcholine.
- **Pharmacokinetics:**
  - **Half-life:** ~66 hours (long, allowing once-daily dosing).
  - **Metabolism:** CYP2D6 (major), CYP3A4/2C19 (minor).
  - **Steady state:** reached in ~2 weeks.

Therapeutic Indications

FDA approved

- **Major Depressive Disorder (MDD)** in adults.

Off-label / studied indications

- Generalized anxiety disorder (mixed evidence).
- Cognitive dysfunction associated with depression.
- OCD, ADHD, and anxiety disorders (investigational, not routinely recommended).

Dosing Guidelines

Adults

- **Starting dose:** 10 mg once daily (with or without food).
- **Target dose:** 20 mg once daily (commonly titrated after 1–2 weeks if tolerated).
- **Dose range:** 5–20 mg daily.
  - 5 mg/day may be used if patients are sensitive to adverse effects.
  - 20 mg/day associated with maximal efficacy.

Elderly: Start at **5 mg daily**; cautious titration due to increased sensitivity.

Hepatic impairment: No adjustment generally required.

Renal impairment

- Mild–severe: no dose adjustment, but limited data in end-stage renal disease.

CYP2D6 poor metabolizers

- Consider maximum dose **10 mg/day** due to higher plasma exposure.

Advantages

1. **Efficacy in depression, including cognitive symptoms**
    - Clinical trials suggest benefit on processing speed, executive function, and memory compared with SSRIs.
2. **Favorable tolerability**
    - Generally, well tolerated; common side effect is nausea (usually transient).
    - **Low risk of sexual dysfunction** compared to SSRIs/SNRIs (though not absent).
    - Minimal weight gain risk.
3. **Low discontinuation symptoms**
    - Long half-life reduces risk of withdrawal compared to Paroxetine or Venlafaxine.
4. **Once-daily dosing**, Improves adherence.
5. **Minimal CYP450 inhibition**
    - Lower drug–drug interaction potential than fluoxetine or paroxetine.

Safety Profile

- **Common adverse effects:** nausea, vomiting, constipation, dizziness, pruritus.
- **Less common:** sexual dysfunction, abnormal dreams, dry mouth.
- **Serious but rare:** serotonin syndrome, hyponatremia/SIADH, angle-closure glaucoma.
- **Boxed warning:** suicidal thoughts and behaviors in children, adolescents, and young adults (as with all antidepressants).

Monitoring

- **Baseline/ongoing:** mood, suicidality, weight, sexual side effects, hyponatremia risk in elderly, drug–drug interactions (esp. CYP2D6 substrates/inhibitors).
- **No routine lab monitoring** required beyond general depression management.

Clinical Pearls

- Useful in patients with **MDD plus cognitive complaints**.
- Preferred when **sexual dysfunction** or **weight gain** are major concerns.
- Can be switched relatively safely due to long half-life; tapering usually not required.
- Avoid co-administration with strong **CYP2D6 inhibitors** (e.g., Bupropion, Fluoxetine, Paroxetine) without dose adjustments.

Summary:

Vortioxetine is a **novel multimodal antidepressant** approved for **MDD in adults**, offering advantages over traditional SSRIs/SNRIs by targeting both mood and cognitive domains, with **lower risks of sexual dysfunction, weight gain, and discontinuation syndrome**. It is administered once daily (5–20 mg), with **10–20 mg/day** being the most effective range.

Mirtazapine **(Remeron®)**

℞ ***Remeron*** *30 mg Tab.*
℞ ***Mirtimash*** *30 mg Tab.*

Pharmacology

- **Class:** Noradrenergic and Specific Serotonergic Antidepressant (NaSSA).
- **Mechanism of action:**
  - ✓ **α_2-adrenergic antagonist** → increases release of norepinephrine (NE) and serotonin (5-HT).
  - ✓ **5-HT_2 and 5-HT_3 antagonist** → enhances transmission via **5-HT_1A receptors** (mood benefits, reduced anxiety, and fewer GI/sexual side effects compared to SSRIs/SNRIs).
  - ✓ **Potent H_1 histamine antagonist** → strong sedative and appetite-stimulating effects.
- **Pharmacokinetics:**
  - ✓ Half-life: ~20–40 hours (once-daily dosing).
  - ✓ Metabolized in the liver.

FDA-Approved Indication

- Major Depressive Disorder (MDD).

Off-Label / Evidence-Supported Uses

- Insomnia (especially with comorbid depression/anxiety).
- GAD, PTSD, Panic Disorder, OCD (evidence-based but not first-line).
- Cancer-related cachexia / appetite stimulation.
- Hot flashes in menopause.
- Adjunct in treatment-resistant depression (augmentation with SSRIs/SNRIs, lithium, antipsychotics, etc.).

Dosing Guidelines

A. Major Depressive Disorder

- **Initial:** 15 mg orally once daily, usually at bedtime
- Increase by 15 mg every 1–2 weeks as tolerated.
- **Therapeutic range:** 15–45 mg once daily.
- **Max dose:** 45 mg/day.

B. Insomnia / Appetite stimulation (off-label)

- Low doses (7.5–15 mg HS) → maximize **H_1 blockade** → sedation, appetite increase.

C. Special Populations

- **Renal impairment:** Dose reduction recommended.
- **Hepatic impairment:** Lower starting doses, cautious titration.
- **Elderly:** Start at lowest effective dose (7.5–15 mg).

Advantages

1. **Sedative benefit**
    - Strong antihistaminic action → excellent choice for patients with depression + insomnia or agitation.
2. **Appetite stimulation / weight gain**
    - Useful in depressed patients with poor appetite, anorexia, cachexia (oncology/palliative settings).
3. **Fewer sexual side effects**
    - Unlike SSRIs/SNRIs, due to 5-HT_2/5-HT_3 antagonism.
4. **Anxiolytic properties**
    - Effective in depression with prominent anxiety symptoms; some evidence supports efficacy in PTSD and GAD.
5. **Rapid onset of action (relative to SSRIs)**
    - Sedative and anxiolytic effects may appear within days, improving adherence.
6. **Low risk of nausea/diarrhea**
    - 5-HT_3 antagonism reduces GI side effects common with SSRIs/SNRIs.
7. **Augmentation role**
    - Often combined with SSRIs/SNRIs ("California rocket fuel": venlafaxine + mirtazapine) in treatment-resistant depression.

Safety & Adverse Effects

- **Common:** Sedation, weight gain, increased appetite, dry mouth, dizziness, constipation.
- **Serious but rare:**
    - Agranulocytosis / neutropenia (requires monitoring if infection symptoms develop).
    - Seizure risk (rare).
    - Serotonin syndrome (especially with other serotonergic agents).
- **Metabolic effects:** Can contribute to weight gain, hyperlipidemia, metabolic syndrome (monitor BMI, lipids, glucose).
- **Suicidality warning:** Same as other antidepressants in youth and young adults.

Monitoring

- Weight, BMI, lipids, and glucose periodically.
- Monitor CBC if symptoms of infection develop.
- Mood, suicidality, and adherence.

Clinical Pearls

- **Lower doses (7.5–15 mg)** = stronger sedation (H_1 effect).
- **Higher doses (30–45 mg)** = less sedation, more noradrenergic activation.
- Best for **patients with depression + insomnia + poor appetite/weight loss.**
- Not ideal in **obese patients, metabolic syndrome, or those concerned about weight gain.**
- Can be combined with SSRIs/SNRIs for **treatment-resistant depression** (synergistic mechanism).

Summary:

Mirtazapine is a **NaSSA antidepressant** uniquely effective in depression with **insomnia, anxiety, or appetite loss**. It offers **advantages over SSRIs/SNRIs** in terms of sedation, appetite stimulation, faster anxiolytic effect, and fewer sexual/GI side effects. However, clinicians must balance benefits with risks of **weight gain, sedation, and metabolic changes**, and monitor appropriately.

Bupropion

℞ ***Wellinta*** **150** mg Tab.

Pharmacology

- **Class:** Norepinephrine–Dopamine Reuptake Inhibitor (NDRI).
- **Mechanism of Action:**
  - Inhibits reuptake of **norepinephrine (NE)** and **dopamine (DA)** via NET and DAT blockade.
  - Minimal effect on serotonin reuptake (distinguishes it from SSRIs/SNRIs).
  - **Nicotinic acetylcholine receptor antagonist** → aids in smoking cessation.
- **Pharmacokinetics:**
  - Bioavailability: ~5–20% (significant first-pass metabolism).
  - Peak plasma concentration: 2–3 h (IR), 5 h (SR), 5–12 h (XL).
  - Metabolism: Hepatic (CYP2B6 → active metabolites).
  - Elimination half-life: Parent ~14 h; metabolites up to 20–37 h.
  - Excretion: Renal (~87%) and fecal (~10%).

Psychiatric Indications

Approved Uses

1. Major Depressive Disorder (MDD) – monotherapy or adjunctive.
2. Seasonal Affective Disorder (SAD) – prophylaxis during winter months.
3. Smoking cessation – via nicotinic antagonism (as Zyban).

Off-label / Investigational Uses

- Bipolar depression (adjunct) – lower risk of inducing mania compared to SSRIs.
- ADHD – alternative to stimulants, especially in adults.
- SSRI/SNRI-induced sexual dysfunction – often used as an augmenting agent.
- Obesity and binge-eating – synergistic in combination with naltrexone (Contrave).
- Negative symptoms of schizophrenia – limited evidence of benefit.

Dosage and Administration

- **Formulations:** Immediate-release (IR), sustained-release (SR), extended-release (XL).

Adults – Depression

- **IR:** Start 100 mg BID; may ↑ to 100 mg TID (max 450 mg/day, single dose ≤150 mg).
- **SR:** Start 150 mg QAM × 3 days → then 150 mg BID (max 400 mg/day, divided BID).
- **XL:** Start 150 mg QD → titrate to 300 mg QD (max 450 mg/day QD).

Smoking Cessation

- 150 mg QAM × 3 days → 150 mg BID (start 1–2 weeks before quit date).

Seasonal Affective Disorder

- Begin in autumn, 150 mg QAM → 300 mg QD, taper in spring. (**QAM = *quaque ante meridiem*** (Latin) → **"every morning).. QD = *quaque die* (Latin) → "once daily"**

Advantages

1. **Non-sedating & activating** → useful for patients with fatigue, hypersomnia, or low energy.
2. **Weight neutral / weight loss potential** → unlike SSRIs, mirtazapine, antipsychotics.
3. **Sexual side effect–sparing** → preferred in patients with SSRI-induced dysfunction.
4. **Smoking cessation aid** → dual psychiatric and medical benefit.
5. **Low risk of mania switch** in bipolar depression compared with SSRIs/SNRIs.
6. **No serotonergic effects** → no serotonin syndrome risk in monotherapy, safer in polypharmacy.
7. **Augmentation option** → can be combined with SSRIs/SNRIs for partial responders.

Adverse Effects & Limitations

- **Common:** Insomnia, headache, dry mouth, nausea, tremor, agitation, anxiety.
- **Seizure risk:** Dose-dependent; incidence ~0.4% at ≤450 mg/day; ↑ with eating disorders, alcohol/benzo withdrawal, or high doses.
- **Hypertension:** Monitor BP, especially with high doses or stimulant combinations.
- **Neuropsychiatric effects:** Anxiety, irritability, psychosis (rare, usually in predisposed patients).
- **Contraindications:**
    - Seizure disorder.
    - Bulimia or anorexia nervosa.
    - Abrupt alcohol/benzodiazepine/sedative withdrawal.
    - Concurrent MAOI use (within 14 days).
- **Renal/hepatic impairment:** Lower starting doses, slower titration.
- **Avoid bedtime dosing** → may cause insomnia.

Monitoring

- **Baseline & follow-up:**
    - Blood pressure (risk of hypertension).
    - Weight, mood, suicidality.
    - Seizure risk factors (e.g., eating disorder, substance withdrawal).

Clinical Pearls

- Good choice for **patients with depression + fatigue, hypersomnia, low motivation, or sexual side effects** from SSRIs.
- Useful in **smokers with depression** (one drug for two targets).
- Often combined with **SSRIs (e.g., fluoxetine, sertraline)** to balance side effects and enhance efficacy.
- Avoid in patients with **anxiety disorders predominance** → may worsen jitteriness/agitation.
- Safer option than stimulants for **ADHD in adults with substance use disorder risk**.

Summary

Bupropion is a unique antidepressant with noradrenergic-dopaminergic action, offering distinct advantages over SSRIs/SNRIs, including stimulant-like energizing effects, weight neutrality, minimal sexual dysfunction, and smoking cessation benefit.

Its main limitations are dose-dependent seizure risk, insomnia, and contraindications in eating disorders or seizure-prone patients.

Clinically, it is valuable as monotherapy for MDD/SAD, an adjunct to SSRIs/SNRIs, and a first-line aid for smoking cessation.

Valproate (Psychiatric Use)

- ℞ ***Depakine*** *200 mg oral Soln.*
- ℞ ***Depakine*** *200 mg Tab*
- ℞ ***Depakine Chrono*** *500 mg Tab*

Pharmacology

- **Class:** Anticonvulsant, mood stabilizer.
- **Mechanism of Action (multi-targeted):**
  - ↑ **GABAergic transmission** → by inhibiting GABA transaminase and increasing glutamic acid decarboxylase activity.
  - **Blockade of voltage-gated sodium channels** → stabilizes neuronal firing.
  - **Inhibition of T-type calcium channels.**
  - **Epigenetic effects** via histone deacetylase (HDAC) inhibition (linked to mood stabilization, neuroprotection).
- **Pharmacokinetics:**
  - Half-life: 8–20 hours (longer with chronic dosing).
  - Metabolism: Hepatic.
  - Protein binding: ~90%.

Psychiatric Indications

- **FDA approved:**
  - **Bipolar disorder:**
    - Acute mania.
    - Mixed episodes.
    - Maintenance (relapse prevention).
- **Off-label (evidence-supported):**
  - Schizoaffective disorder (as mood stabilizer).
  - Adjunct in treatment-resistant schizophrenia (especially with aggression, impulsivity, affective instability).
  - Impulse control disorders (intermittent explosive disorder, borderline personality disorder with aggression).
  - Adjunct in PTSD, agitation, and irritability (esp. in TBI, dementia).
  - Rapid-cycling bipolar disorder.

Dosage and Administration

- **Formulations:** Sodium valproate, valproic acid, and divalproex sodium (enteric-coated or extended-release).
- **Bipolar disorder (adults):**
  - Initial: 250–500 mg PO BID–TID.
  - Rapid loading (for acute mania): 20 mg/kg/day divided doses (well tolerated in acute setting).
  - Maintenance: 750–2500 mg/day (commonly 1000–2000 mg/day).
  - Target plasma level: 50–125 μg/mL (therapeutic range for mania).
- **Elderly:** Lower doses (250–500 mg/day initially), titrate slowly.
- **Pediatric (mania):** 10–15 mg/kg/day initial; titrate up to 60 mg/kg/day max.

Advantages in Psychiatry

1. **Broad-spectrum mood stabilizer:** Effective for **mania, mixed states, and rapid cycling** (where lithium is less effective).
2. **Rapid onset of action** in acute mania compared to lithium (often improves symptoms in 3–5 days).
3. **Well tolerated in aggression, impulsivity, and irritability** (esp. in BPD, dementia, TBI).
4. **Can be combined safely with antipsychotics** for acute mania or schizoaffective disorder.
5. **Less risk of renal toxicity and thyroid dysfunction** compared to lithium.
6. **Useful in comorbid epilepsy or migraine** (dual benefit).
7. **Better tolerated than carbamazepine** (less risk of drug interactions, SJS, hematologic toxicity).

Limitations & Adverse Effects

- **Common:** Weight gain, sedation, tremor, GI upset (nausea, vomiting), alopecia.
- **Neurological:** Ataxia, dizziness, cognitive dulling.
- **Endocrine/metabolic:** Hyperinsulinemia, metabolic syndrome, PCOS (esp. in young women).
- **Hepatic toxicity:** Elevated LFTs, rare fatal hepatotoxicity (highest risk <2 years old).
- **Pancreatitis (rare, life-threatening).**
- **Hematologic:** Thrombocytopenia, leukopenia.
- **Hyperammonemia** → encephalopathy (esp. with carnitine deficiency).
- **Teratogenicity:**
  - Major malformations (esp. **neural tube defects, spina bifida**).
  - Cognitive impairment and autism risk in exposed children.
  - **Contraindicated in women of childbearing potential unless no alternatives.**

Monitoring

- **Baseline:** CBC, LFTs, electrolytes, pregnancy test (women of childbearing potential), weight/BMI.
- **Follow-up:**
    - **Plasma valproate levels** (therapeutic: 50–125 μg/mL; toxic >150 μg/mL).
    - **LFTs and CBC** every 3–6 months.
    - **Ammonia** if mental status changes.
    - **Metabolic monitoring** (weight, glucose, lipids).

Clinical Pearls

- **Best for acute mania and mixed states** (lithium better for classic mania, less effective in mixed/rapid cycling).
- **Combination therapy** (Valproate + Antipsychotic) is standard for **severe mania**.
- **Loading dose strategy (20 mg/kg)** → rapid stabilization in acute mania.
- **Avoid in pregnancy** (Category X in most guidelines, unless life-threatening psychiatric state).
- **Switch to lithium or lamotrigine** if long-term maintenance needed in women of reproductive age.
- **Carnitine supplementation** may reduce hyperammonemia risk.

Summary:

Valproate is a **broad-spectrum mood stabilizer** with **strong efficacy in acute mania, mixed states, rapid cycling, aggression, and impulsivity**.

It is often used **in combination with antipsychotics** in severe cases and is better tolerated than carbamazepine.

Its **major advantages** are rapid onset, wide efficacy across mood disorders, and tolerability in renal disease.

Its **main drawbacks** are **hepatotoxicity, teratogenicity, metabolic side effects, and hyperammonemia**, requiring careful monitoring.

Lithium

℞ ***Prianil CR*** *400 mg Tab.*

℞ ***Lithiomod*** *400 mg Tab*

Pharmacology

- **Class:** Mood stabilizer (first-line, gold standard).
- **Mechanism of Action:**
  - Exact mechanism is not fully understood, but involves:
    - **Inhibition of inositol monophosphatase** → ↓ phosphoinositide signaling.
    - **Modulation of glycogen synthase kinase** → effects on neuroplasticity.
    - **Influence on circadian rhythms.**
    - **Neuroprotective actions** (increases gray matter volume, enhances BDNF expression).
- **Pharmacokinetics:**
  - Oral absorption: rapid and complete.
  - Distribution: widely, no protein binding.
  - Half-life: 18–24 hours (longer in elderly, up to 36 hrs.)
  - Excretion: **renal (100%)**, no hepatic metabolism.
  - Narrow therapeutic index → requires **serum level monitoring**.

Psychiatric Indications

- **Approved / First-line:**
  - **Bipolar disorder**:
    - Acute mania (especially euphoric mania).
    - Bipolar depression (less potent than in mania, but effective).
    - Maintenance therapy (relapse prevention, both mania and depression).
  - **Suicide prevention** in mood disorders → only mood stabilizer with robust evidence for anti-suicidal effect.
- **Other indications:**
  - **Augmentation in treatment-resistant depression** (low-dose adjunct to antidepressants).
  - **Schizoaffective disorder** (adjunct).
  - **Aggression and impulsivity** (personality disorders, intellectual disability, TBI).
- **Off-label / investigational:**
  - Cluster headaches, Huntington's disease, certain neurodegenerative conditions.

Dosage and Administration

- **Formulations:** Lithium carbonate (immediate-release, sustained-release), lithium citrate solution.
- **Initial dose (adults):**
  - 300 mg PO 2–3 times daily; adjust according to serum levels.
- **Maintenance dose:**
  - Typically, 900–1800 mg/day in divided doses.
- **Target serum levels:**
  - Acute mania: 0.8–1.2 mEq/L.
  - Maintenance: 0.6–1.0 mEq/L.
  - Elderly or medically frail: 0.4–0.8 mEq/L.
- **Onset of action:**
  - Mania: 7–10 days (often requires antipsychotic/benzodiazepine bridging).

Advantages in Psychiatry

1. **Gold-standard mood stabilizer** → strongest evidence for **long-term prophylaxis** in bipolar disorder.
2. **Only agent with proven anti-suicidal effect** in mood disorders.
3. **Effective in both mania and depression**
4. **Neuroprotective and neurotrophic effects** (may reduce progression of cognitive decline).
5. **Simple metabolism** (renal excretion, no hepatic metabolism → safer in hepatic impairment).
6. **Effective augmentation agent** in treatment-resistant depression.

Limitations & Adverse Effects

- **Narrow therapeutic index** → requires frequent monitoring.
- **Common side effects:** Tremor, polyuria, polydipsia, weight gain, GI upset, metallic taste.
- **Endocrine/metabolic:**
  - **Hypothyroidism** (5–30%).
  - **Goiter.**
  - **Hyperparathyroidism → hypercalcemia.**
- **Renal:** Nephrogenic diabetes insipidus.
- **Neurological:** Fine tremor (common), cognitive dulling.
- **Cardiac:** T-wave flattening/inversion, sinus node dysfunction (contraindicated in severe cardiac disease).
- **Pregnancy risks:** Floppy baby syndrome, neonatal hypothyroidism.
- **Toxicity (levels >1.5 mEq/L):** Coarse tremor, ataxia, confusion, GI upset, seizures, coma → life-threatening.

Monitoring

- **Before initiation:**
  - Renal function (BUN, creatinine, eGFR).
  - Thyroid function (TSH, free T_4).
  - Calcium levels (parathyroid function).
  - CBC, weight, ECG (if >40 yrs or cardiac disease), pregnancy test (women of childbearing potential).
- **During treatment:**
  - **Lithium levels:** 5–7 days after initiation or dose change; then every 3 months (maintenance).
  - **Renal and thyroid function:** Every 6–12 months.
  - **Calcium, weight, metabolic monitoring:** Periodically.

Clinical Pearls

- **Best efficacy in:**
  - **Euphoric mania** (less effective in mixed states or rapid cycling compared to valproate).
  - **Classic episodic bipolar disorder with clear inter-episode recovery.**
- **Anti-suicidal property** makes it the preferred agent in high-risk patients.
- **Combination therapy**: Lithium + Antipsychotic or Valproate often used in severe mania.
- **Drug interactions:**
  - NSAIDs, ACE inhibitors, thiazide diuretics ↑ lithium levels → toxicity risk.
  - Caffeine, theophylline ↓ lithium levels.
- **Hydration is crucial**: dehydration, salt restriction, or renal impairment can increase toxicity risk.

Summary:

Lithium remains the **gold standard mood stabilizer** in psychiatry, with unmatched evidence for **long-term prophylaxis in bipolar disorder and suicide prevention**. It is effective in both mania and depression, inexpensive, and neuroprotective. Its drawbacks are a **narrow therapeutic index, renal and thyroid toxicity, and teratogenic risk**, requiring careful monitoring and patient education.

Topiramate (Psychiatric Applications)

- ℞ ***Topamax*** *15 - 25 - 50 - 100 mg Tab.*
- ℞ ***Conviban*** *25-30-100 mg Tab*
- ℞ ***Topiramate*** *25-100-200 mg Tab*

Pharmacology

- **Class:** Anticonvulsant (structurally a sulfamate-substituted monosaccharide).
- **Mechanisms of Action (multi-targeted):**
  - Blocks **voltage-dependent sodium channels** → stabilizes neuronal excitability.
  - **Enhances GABA-A receptor activity** (increased inhibitory neurotransmission).
  - **Antagonizes AMPA/kainate glutamate receptors** → reduces excitatory transmission.
  - **Inhibits carbonic anhydrase isoenzymes II & IV** → mild metabolic acidosis, appetite suppression.
- **Pharmacokinetics:**
  - Half-life: ~21 hours.
  - Metabolism: partly hepatic; ~70% excreted unchanged in urine.

Psychiatric Indications

Topiramate is **not FDA-approved for psychiatric disorders**, but has evidence for several **off-label uses**:

Evidence-Supported Indications

- **Bipolar disorder (adjunct):**
  - Limited efficacy as monotherapy, but may be used as add-on for **mania or mixed states**, especially in overweight/metabolic syndrome patients.
- **Alcohol use disorder:** Reduces cravings, alcohol consumption, and risk of relapse (via GABA/glutamate modulation).
- **Binge eating disorder & bulimia nervosa:** Reduces binge frequency, weight, and food cravings.
- **Obesity associated with psychiatric illness:**
  - Used as adjunct to antipsychotics (especially olanzapine, clozapine) to mitigate weight gain.
- **Impulse control disorders, aggression, anger dysregulation, reducing self-mutilating behaviors:**
  - Some benefit in borderline personality disorder and TBI-related aggression.
- **PTSD (adjunct):**
  - Evidence for improvement in re-experiencing and hyperarousal symptoms.
- **Cocaine dependence, smoking cessation (limited but emerging evidence).**
- Migraine prevention, essential tremors.

Dosage and Administration

- **General psychiatric dosing:**
  - **Start:** 25 mg PO at bedtime.
  - **Titrate:** Increase by 25–50 mg every 3–7 days.
  - **Target dose: 100–300 mg/day** (divided BID).
- **Alcohol use disorder:** Often 200–300 mg/day effective.
- **Binge eating disorder/obesity:** 100–200 mg/day.
- **Maximum recommended dose:** 400 mg/day (higher doses not well tolerated).
- **Renal impairment:** Dose reduction required (clearance ↓).

Advantages in Psychiatry

1. **Weight loss and appetite suppression** → unique benefit compared to other mood stabilizers (useful with antipsychotic-associated weight gain, obesity, binge eating).
2. **Low risk of metabolic syndrome** (opposite of valproate/olanzapine).
3. **Helpful in substance use disorders** (alcohol, cocaine).
4. **Adjunctive role in aggression, impulsivity, PTSD** where traditional mood stabilizers may be limited.
5. **Dual benefit in comorbid epilepsy or migraine**.
6. **No hematologic or hepatic toxicity** (unlike carbamazepine, valproate, clozapine).

Limitations & Adverse Effects

- **Cognitive adverse effects:** Attention, memory, and word-finding difficulties ("Dopamax" nickname).
- **Neurological:** Paresthesia (common, due to carbonic anhydrase inhibition), fatigue, psychomotor slowing.
- **Metabolic:**
  - Weight loss (benefit, but excessive in some).
  - Metabolic acidosis (rare but relevant in renal impairment).
- **Renal:** Kidney stones (~1–2% risk, especially with dehydration).
- **Ophthalmologic:** Acute angle-closure glaucoma (rare, but serious).
- **Psychiatric:** Can worsen depression, anxiety, or psychosis in some cases.
- **Teratogenicity:** ↑ risk of oral clefts when used in pregnancy.

Monitoring

- **Baseline:** Weight, electrolytes, bicarbonate, renal function.
- **During treatment:**
    - Periodic electrolytes and bicarbonate (esp. if symptomatic or high doses).
    - Weight monitoring.
    - Cognitive status (subjective/objective).
    - Ophthalmologic symptoms (acute vision changes).

Clinical Pearls

- Best considered an **adjunctive agent**, not a primary mood stabilizer.
- **Useful for overweight bipolar patients** needing both mood stabilization and weight control.
- **Combination therapy:** Can be combined with lithium, valproate, or antipsychotics.
- **Slow titration** minimizes cognitive and neurological side effects.
- **Hydration is important** → reduces kidney stone risk.
- Avoid in patients with **history of nephrolithiasis, glaucoma, or severe depression**.

Summary:

Topiramate is a **broad-acting anticonvulsant** with important **psychiatric off-label applications**: adjunctive treatment in **bipolar disorder, alcohol use disorder, binge eating, obesity, PTSD, and impulsivity/aggression**. Its **major advantage** is weight loss and reduction of cravings, making it particularly useful in patients with **antipsychotic-induced weight gain or comorbid obesity/substance use**.

Its **limitations** include cognitive side effects, kidney stone risk, and lack of robust efficacy as a primary mood stabilizer.

Lamotrigine (Psychiatric Use)

℞ ***Lamictal*** *2 - 25 - 50 - 100 mg Tab.*
℞ ***Conviban*** *25-50-100 mg Tab*

Pharmacology

- **Class:** Anticonvulsant, mood stabilizer.
- **Mechanism of Action:**
  - **Blocks voltage-gated sodium channels** → inhibits excessive glutamate and aspartate release.
  - **Stabilizes neuronal membranes** and prevents excitotoxicity.
  - **Modulates glutamatergic transmission** more than GABAergic.
- **Pharmacokinetics:**
  - Half-life: 25–33 hours (↑ with Valproate, ↓ with Carbamazepine, Phenytoin).
  - Metabolism: Hepatic (via glucuronidation).
  - Excretion: Renal.

Psychiatric Indications

Approved / Guideline-supported

- **Bipolar I disorder**:
  - **Maintenance therapy** (effective in preventing depressive episodes, less so for mania).

Off-label / Evidence-supported

- **Bipolar II disorder**: Strong efficacy in **bipolar depression** prevention.
- **Acute bipolar depression** (used clinically, though evidence modest vs. placebo).
- **Treatment-resistant unipolar depression** (augmentation strategy).
- **Schizoaffective disorder / depressive symptoms in schizophrenia.**
- **Borderline personality disorder (BPD)** → evidence for mood lability, impulsivity (not first-line).
- **PTSD (adjunct).**

Dosage and Administration

- **Key principle: Slow titration** to minimize risk of Stevens–Johnson syndrome (SJS).

Typical Bipolar Disorder Dosing (Adults)

- **Start:** 25 mg PO daily × 2 weeks.
- Then 50 mg daily × 2 weeks.
- Then 100 mg daily × 1 week.
- **Maintenance:** 200 mg/day (usual effective range: 100–400 mg/day).

Special cases

- **With valproate:**
  - Halve dose → start 25 mg every other day × 2 weeks, max 100 mg/day.
- **With enzyme inducers (e.g., Carbamazepine, Phenytoin):**
  - Double dose → faster clearance, target 300–500 mg/day.
- **Elderly:** Lower initial doses; titrate cautiously.

Advantages in Psychiatry

1. **Strong efficacy in bipolar depression prevention** (unique among mood stabilizers, as lithium and valproate are stronger for mania).
2. **Well tolerated metabolically** → weight-neutral, no dyslipidemia, no insulin resistance.
3. **Cognitive profile is favorable** (does not cause dulling like topiramate/valproate).
4. **Safer in pregnancy than Valproate/Carbamazepine** (but not completely risk-free).
5. **Minimal drug–drug interactions** compared to carbamazepine, valproate.
6. **Useful as augmentation in resistant depression** when SSRIs/SNRIs insufficient.
7. **Not sedating** → good option in patients with fatigue or hypersomnia.

Limitations & Adverse Effects

- **Most serious:** Stevens–Johnson syndrome (SJS) / Toxic epidermal necrolysis (TEN).
  - Risk ↑ with rapid titration, coadministration with valproate, high initial dose.
- **Common side effects:** Headache, dizziness, diplopia, insomnia, nausea.
- **Psychiatric:** May cause agitation, irritability in some patients.
- **Other:** Rare hematological (neutropenia), aseptic meningitis.
- **Not effective for acute mania** (needs adjunct with antipsychotics/valproate/lithium).
- **Pregnancy:** Relatively safer, but possible risk of oral clefts in first trimester.

Monitoring

- No routine serum levels required (unlike lithium/valproate).
- **Baseline:** Skin exam, medication reconciliation (for drug interactions).
- **Ongoing:**
  - Watch for rash, especially in first 8 weeks.
  - Monitor mood charting (depression/mania prevention).
  - Dose adjustments with interacting AEDs.

Clinical Pearls

- **Best for bipolar patients with predominant depressive polarity** or **rapid cycling with depression**.
- **Not useful alone for mania** → combine with lithium/valproate/antipsychotic if needed.
- **Adherence-critical:** Missed doses (>5 half-lives) may require **re-titration** to reduce rash risk.
- **Pregnancy:** Preferred over valproate; but dose ↑ may be needed due to ↑ clearance.
- **Combination therapy:**
    - **Lithium + Lamotrigine** → strong evidence for preventing both mania (lithium) and depression (lamotrigine).
    - **Valproate + Lamotrigine** → effective but requires extra caution for SJS.

Summary

Lamotrigine is a **modern mood stabilizer** with **unique efficacy in preventing bipolar depression**, where other agents are less effective.

It is **weight-neutral, cognitively sparing, and relatively safe in pregnancy**, making it highly suitable for **long-term maintenance in bipolar II disorder, rapid cycling, and depression-predominant bipolar I disorder**.

Its **main limitation** is the risk of **severe rash (SJS/TEN)**, necessitating **slow titration and careful monitoring**.

It is **not effective for acute mania**, so best used in **maintenance or as adjunctive therapy**.

Stevens-Johnson syndrome (SJS) is a severe, potentially fatal allergic reaction primarily triggered by medications or infections, causing painful blisters and lesions on the skin and mucous membranes. It is considered a life-threatening skin disorder characterized by flu-like symptoms followed by a widespread red rash, blistering, and peeling skin, particularly affecting the eyes, mouth, and genitals. SJS is the less severe end of a spectrum that also includes toxic epidermal necrolysis (TEN), with treatment focused on supportive care in a burn unit, including stopping the offending agent and managing complications like fluid loss and infection.

Symptoms

SJS typically starts with symptoms similar to the flu, including: fever, sore throat, cough, and body aches, soon followed by:

- A widespread, painful red or purple rash: that can resemble a sunburn or have a target-like appearance.
- Blisters and sores: on the skin and mucous membranes (mouth, eyes, genitals).
- Peeling and shedding of the skin.
- Eye problems, including severe pain, swelling, and crusting.
- Difficulty eating: due to sores in the mouth and throat.
- Painful urination: from affected mucous membranes in the genitals.

Treatment and Management

- **Hospitalization:** Patients are typically hospitalized, often in a burn unit, due to the severity of the skin damage.
- **Supportive Care:** Treatment focuses on supportive measures like fluids, pain management, and preventing infection.
- **Medications:** In some cases, corticosteroids, cyclosporine, or intravenous immune globulin (IVIG) may be used.

Oxcarbazepine - (Psychiatric Use)

- ℞ ***Trileptal*** 60 mg/ml oral Susp.
- ℞ ***Trileptal*** 150-300-600 mg Tab.
- ℞ ***Oxaleptal*** 300-600 mg Tab.

Pharmacology

- **Class:** Anticonvulsant, structural analog of carbamazepine.
- **Prodrug:** Rapidly converted to active metabolite **10-monohydroxy derivative (MHD)**.
- **Mechanisms of Action:**
  - **Blocks voltage-gated sodium channels** → reduces neuronal excitability.
  - **Modulates voltage-gated calcium channels.**
  - **Enhances potassium conductance.**
  - Indirect effects on glutamatergic and GABAergic neurotransmission.
- **Pharmacokinetics:**
  - Half-life: Parent ~2 h; active metabolite MHD ~9–10 h.
  - Metabolism: Hepatic (non-CYP oxidation → less drug interactions than carbamazepine).
  - Excretion: Renal (mainly as metabolites).

Psychiatric Indications

Evidence-Supported / Off-label

- **Bipolar disorder:**
  - Studied as alternative to carbamazepine/valproate.
  - Some efficacy in **acute mania**; less robust for maintenance or bipolar depression.
- **Schizoaffective disorder / schizophrenia adjunct:** Limited evidence for mood stabilization and aggression control.
- **Impulse control and aggression:**
  - Reported benefits in **intermittent explosive disorder, BPD, intellectual disability, TBI-related aggression**.
- **Alcohol withdrawal / dependence:** Some evidence for reducing withdrawal symptoms and cravings.
- **Neuropathic pain, irritability, and mood instability** in psychiatric comorbidities.

Note: Oxcarbazepine is **not FDA-approved for psychiatric indications**; its use is off-label, guided by clinical judgment and local guidelines.

Dosage and Administration

- **Adult dosing (psychiatric use):**
  - Start: 150–300 mg twice daily.
  - Titration: Increase by 300 mg/day every 3–7 days as tolerated.
  - Typical effective range: 900–2400 mg/day (divided BID).
  - Max dose: 2400 mg/day.
- Elderly / renal impairment: Start lower (150 mg BID), titrate slowly.
- Therapeutic drug monitoring: Not routinely required (unlike lithium, valproate).

Advantages in Psychiatry

1. **Better tolerability than carbamazepine:**
   - Lower risk of hematologic toxicity (no agranulocytosis/aplastic anemia).
   - Lower risk of hepatic enzyme induction.
2. **Fewer drug–drug interactions:** Minimal CYP450 induction → safer in polypharmacy.
3. **Effective in acute mania and aggression** in some patients, especially when lithium or valproate are poorly tolerated.
4. **No need for serum level monitoring** (unlike lithium/valproate/carbamazepine).
5. **Dual benefit in epilepsy or neuropathic pain** comorbid with psychiatric disorders.
6. **Safer in hepatic disease** compared to valproate or carbamazepine (since mostly renal clearance).

Limitations & Adverse Effects

- **Common:** Dizziness, somnolence, headache, nausea, fatigue.
- **Neurological:** Ataxia, diplopia, sedation.
- **Hyponatremia (SIADH):** Most clinically significant adverse effect; risk ↑ in elderly and at high doses.
- **Dermatological:** Rash (less than carbamazepine, but possible SJS/TEN).
- **Endocrine/metabolic:** Mild weight gain (less than valproate, atypical antipsychotics).
- **Psychiatric:** Rare reports of irritability, anxiety, or mood worsening.
- **Pregnancy:** Possible teratogenicity (oral clefts, neural tube defects) → avoid if alternatives available.

Monitoring

- **Baseline:** Sodium, renal function, LFTs, CBC.
- **Ongoing:**
  - **Serum sodium** (esp. in elderly, renal disease, polypharmacy with SSRIs/diuretics).
  - Clinical monitoring for rash (esp. first 2 months).

Clinical Pearls

- **Best candidates:**
  - Patients with **acute mania, aggression, or impulsivity**, especially when lithium/valproate are not tolerated.
  - Patients with **hepatic disease or on polypharmacy**, where carbamazepine is problematic.
- **Not first-line for maintenance in bipolar disorder** (evidence weaker than lithium, valproate, lamotrigine).
- **Hyponatremia risk** → caution in elderly, those on SSRIs, thiazides.
- **Adjunct role**: Can be combined with lithium, valproate, or antipsychotics in refractory mania.

Summary

Oxcarbazepine is an **anticonvulsant mood stabilizer** with evidence for **acute mania, aggression, and impulsivity**, though less robust for long-term bipolar maintenance compared to lithium or valproate.

It offers **better tolerability and fewer interactions** than carbamazepine, making it useful in patients with **hepatic impairment or polypharmacy**.

Its **main limitations** are **hyponatremia, dermatologic reactions, and weaker evidence in bipolar depression/maintenance**.

Haloperidol

- ℞ ***Haloperidol*** *5 mg Amp.*
- ℞ ***Haloperidol Retard*** *50 mg Amp.*
- ℞ ***Haloprol Decanoas*** *100mg Amp.*
- ℞ ***Haldol Decanoas*** *50 mg Amp.*

Pharmacology

- **Class:** First-generation antipsychotic (butyrophenone derivative).
- **Mechanism of Action:**
  - **Potent D_2 dopamine receptor antagonist** → strong effect on mesolimbic pathway (reduces positive psychotic symptoms).
  - Minimal serotonergic blockade compared with atypicals → less effective for negative/cognitive symptoms.
  - High-potency FGA → **high EPS risk** but **low anticholinergic, antihistaminic, and α1-adrenergic blockade** compared to low-potency FGAs.
- **Metabolism:** Hepatic.
- **Half-life:** 14–36 h (oral); ~21 days (decanoate LAI).

FDA-Approved Indications

1. Schizophrenia and other psychotic disorders.
2. Acute psychosis (including drug-induced).
3. Tourette's disorder / severe tics.
4. Severe behavioral problems in children (hyperactivity with aggression, explosive outbursts, impulsivity) when other treatments fail.
5. Short-term treatment of severe agitation or acute mania.

Off-Label / Evidence-Supported Uses

- Delirium (acute agitation/confusion in ICU, palliative care).
- Bipolar disorder (acute mania, adjunctive use).
- Nausea/vomiting (esp. chemotherapy-induced, palliative care).
- Huntington's chorea.
- Adjunct in treatment-resistant status epilepticus (control of agitation).

Dosage and Administration

A. **Schizophrenia (Adults)**
   - **Oral:**
     - Initial: 0.5–5 mg two or three times daily.
     - Maintenance: 5–20 mg/day (divided or once daily).
     - Maximum: 30–40 mg/day (rarely >20 mg/day due to EPS risk).
   - **IM short-acting (acute agitation/psychosis):**
     - 2–5 mg every 4–8 h PRN.
     - Max: 20 mg/day.
   - **Long-acting injectable (Haloperidol decanoate):**
     - Initial: 10–20 × previous daily oral dose, given IM every 4 weeks.
     - Usual range: 50–200 mg/month.
     - Oral overlap for 1 month recommended at initiation.

B. **Tourette's Disorder / Tics**
   - Start: 0.5–2 mg/day (divided).
   - Maintenance: 2–10 mg/day.

C. **Pediatric Severe Behavior**
   - Initial: 0.25–0.5 mg/day.
   - Usual effective: 0.05–0.15 mg/kg/day (max 10 mg/day).

Advantages

1. **Potent antipsychotic efficacy** → highly effective in controlling **positive symptoms** (hallucinations, delusions, agitation).
2. **Rapid onset (IM formulation):** Preferred for **acute agitation, psychotic emergencies, and delirium.**
3. **Long-acting injectable (decanoate):** Improves adherence in chronic psychotic disorders.
4. **Less sedation, weight gain, and anticholinergic effects** compared with low-potency FGAs and many Atypicals.
5. **Versatility:** Effective across schizophrenia, mania, delirium, Tourette's, agitation, and nausea.
6. **Low cost & global availability.**

Limitations & Adverse Effects

- **Extrapyramidal symptoms (EPS):**
  - Acute dystonia, akathisia, parkinsonism.
  - Tardive dyskinesia (with long-term use).

- **Neuroleptic Malignant Syndrome (NMS):** Rare but life-threatening.
- **QT prolongation, torsades de pointes, sudden death:** Especially with IV or high doses.
- **Hyperprolactinemia:** Galactorrhea, amenorrhea, gynecomastia, sexual dysfunction.
- **Other:** Insomnia, restlessness, mild sedation.

Monitoring

- **ECG** (baseline and follow-up in patients with cardiac risk/QTc prolongation).
- **AIMS scale** (for tardive dyskinesia/EPS monitoring).
- **Prolactin levels** if symptomatic.
- **Vitals** when using IM for agitation (risk of hypotension/QTc issues).

Clinical Pearls

- **High potency** → more EPS but **less sedation, orthostasis, and anticholinergic burden** compared to chlorpromazine, thioridazine.
- **Best for:**
    - Acute agitation/delirium (IM use).
    - Psychosis when sedation not desired.
    - Patients requiring LAI but not tolerating atypicals.
- **Avoid in:**
    - Patients with Parkinson's disease or Lewy body dementia (worsens motor symptoms).
    - Cardiac conduction abnormalities (QTc prolongation).
- **IM haloperidol** often combined with benzodiazepine (e.g., lorazepam) for rapid tranquilization.

Summary:

Haloperidol is a high-potency typical antipsychotic with strong efficacy in treating acute and chronic psychosis, agitation, and tics. Its parenteral formulations make it invaluable in emergencies, while the long-acting decanoate supports adherence in schizophrenia.

However, it carries a high risk of EPS, tardive dyskinesia, and QT prolongation, requiring careful monitoring. Despite these risks, it remains a cornerstone antipsychotic worldwide due to its efficacy, versatility, and cost-effectiveness.

Chlorpromazine

℞ ***Neurazine 25, 100 mg*** *Tab.*

Pharmacology

- **Class:** First-generation (typical) antipsychotic; phenothiazine derivative.
- **Mechanism of action:**
  - **Strong D_2 receptor antagonism** → antipsychotic efficacy, but high risk of extrapyramidal symptoms (EPS) and hyperprolactinemia.
  - **Antagonism at α_1-adrenergic, H_1-histaminic, and muscarinic receptors** → sedation, orthostatic hypotension, anticholinergic side effects.
  - **Weak 5-HT_2 antagonism** compared to atypical antipsychotics.
- **Pharmacokinetics:**
  - Oral doses usually divided 2–4 times daily
  - Hepatic metabolism (mainly CYP2D6, CYP1A2).
  - Half-life: ~16–30 hours; active metabolites extend duration.

Clinical Uses / Indications

FDA-approved / established uses:

1. **Schizophrenia and other psychotic disorders** (control of positive symptoms, agitation, hallucinations, delusions).
2. **Mania** (short-term control).
3. **Severe behavioral problems in children** (agitation, explosive outbursts).
4. **Intractable hiccups** (low-dose use).
5. **Severe nausea/vomiting** (antiemetic effect).
6. **Tetanus (adjunctive therapy).**

Off-label / occasional uses:

- Huntington's chorea symptoms.
- Palliative care (agitation, nausea).

Dosages

- **Schizophrenia / psychosis (adults):**
  - Initial: 25–50 mg PO 2–3 times/day.
  - Usual effective range: 200–800 mg/day (sometimes higher for resistant cases).
  - IM acute agitation: 25–50 mg q6–8h as needed (max 400 mg/day IM).

- **Hiccups:** 25–50 mg PO q6–8h.
- **Children (behavioral problems, psychosis):**
    - Start 0.5 mg/kg/dose q4–6h; adjust gradually.
    - Typical range: 30–75 mg/day (sometimes up to 200 mg/day depending on age/weight).
- **Elderly:** start low (10–25 mg 2–3 times/day) due to sensitivity to sedation, orthostasis.

Advantages

- **Broad spectrum of use:** psychosis, mania, severe agitation, intractable hiccups, nausea.
- **Multiple routes:** oral, IM, IV.
- **Cost:** inexpensive, widely available.
- **Sedation:** useful when calming effect is desired (acute agitation, palliative care).
- **Long clinical experience:** well-studied and familiar in psychiatry and general medicine.

Limitations & Adverse Effects

- **Neurologic:** high risk of EPS (dystonia, parkinsonism, akathisia, tardive dyskinesia).
- **Endocrine:** hyperprolactinemia → galactorrhea, menstrual changes, sexual dysfunction.
- **Cardiovascular:** QT prolongation, orthostatic hypotension, tachycardia.
- **Metabolic:** weight gain (less than olanzapine/quetiapine but more than haloperidol).
- **Sedation:** often excessive due to H_1 antagonism.
- **Anticholinergic effects:** dry mouth, blurred vision, constipation, urinary retention, cognitive impairment.
- **Hepatic:** cholestatic jaundice (rare, idiosyncratic).
- **Ophthalmologic:** corneal/lens deposits with long-term use.
- **Other:** risk of neuroleptic malignant syndrome (NMS), seizures at high doses.

Summary

Chlorpromazine is a **low-potency typical antipsychotic** with strong sedative, anticholinergic, and autonomic effects. It is effective in **schizophrenia, mania, agitation, hiccups, and severe nausea**, but its use today is limited by **high risk of EPS, cardiovascular, and metabolic side effects** compared to newer agents. It remains useful in acute settings (for sedation and agitation) and in resource-limited contexts due to low cost and availability.

Sulpiride

- ℞ ***Dogmatil Fort*** *200 mg Tab.*
- ℞ ***Dogmatil*** *50 mg Tab.*
- ℞ ***Topmode Fort*** *200 mg Tab.*
- ℞ ***Topmode*** *50 mg Tab.*

Pharmacology

- **Class:** Substituted benzamide antipsychotic (first-generation, but atypical profile at low doses).
- **Mechanism of Action:**
  - ✓ **Selective dopamine D_2/D_3 receptor antagonist** (minimal affinity for D_1, serotonin, histamine, muscarinic, or adrenergic receptors).
  - ✓ **Dose-dependent effects:**
    - Low dose (50–150 mg/day): Prefrontal dopamine autoreceptor blockade → antidepressant, anxiolytic, pro-cognitive effects.
    - Moderate to high dose (200–800 mg/day): Limbic D_2 antagonism → antipsychotic effects.
    - Very high dose (>800–1200 mg/day): Striatal D_2 blockade → ↑ EPS risk.
- **Metabolism:** Minimally hepatic; ~90% excreted unchanged in urine.
- **Half-life:** 6–8 hours.

Approved Indications (varies by country)

1. **Schizophrenia and other psychoses.**
2. **Acute and chronic psychotic states.**
3. **Depression (low-dose, adjunctive in resistant cases).**
4. **Somatic symptom disorders, functional GI syndromes (esp. dyspepsia, IBS, functional dysmotility).**
5. **Vertigo (peripheral and central).**

Off-Label / Evidence-Supported Uses

- Dysthymia, anxiety disorders.
- Negative symptoms of schizophrenia (unique advantage vs. typical antipsychotics).
- Adjunct in Parkinson's disease psychosis (less motor worsening at low doses).
- Migraine prophylaxis (experimental).

Dosage and Administration

A. Schizophrenia / Psychosis (Adults)

- Initial: 200–400 mg/day (divided).
- Usual therapeutic: 400–800 mg/day (divided BID–TID).
- Maximum: 1200–1600 mg/day (rarely used due to EPS).

B. Depression / Dysthymia (Adjunct, Low Dose)

- 50–150 mg/day (once or divided twice daily).

C. Somatic Disorders / Functional GI Syndromes

- 50–100 mg 2–3× daily.

D. Vertigo

- 25–50 mg 2–3× daily.

Advantages

1. **Receptor selectivity:** Minimal anticholinergic, antihistaminic, or adrenergic blockade → **fewer side effects** (sedation, weight gain, orthostasis) compared to most antipsychotics.
2. **Low-dose antidepressant/anxiolytic effect:** Unique among antipsychotics; useful in **somatic symptom disorders, dysthymia, psychosomatic GI disorders.**
3. **Effective for negative symptoms of schizophrenia:** More efficacy in apathy, withdrawal, and affective blunting than typical FGAs.
4. **Lower metabolic burden** than atypical antipsychotics like olanzapine and clozapine.
5. **Well tolerated in elderly and in functional disorders.**
6. **No significant hepatic metabolism:** Advantage in patients with liver disease.

Limitations & Adverse Effects

- Extrapyramidal symptoms (EPS): Dose-dependent, more common at >800 mg/day.
- Hyperprolactinemia: Galactorrhea, amenorrhea, gynecomastia, sexual dysfunction (common due to strong pituitary D_2 blockade).
- Insomnia, agitation, restlessness (esp. at low doses).
- QT prolongation (rare but reported).
- Weight gain: Less than atypicals, but mild-moderate risk.
- CNS: Headache, dizziness, mild sedation.
- Neuroleptic malignant syndrome (rare).
- Contraindicated in renal failure (drug is renally excreted).

Monitoring

- **Renal function (serum creatinine, eGFR)** before initiation and periodically.
- **ECG** (QTc prolongation risk).
- **Prolactin levels** if symptomatic.
- **EPS monitoring (AIMS, Simpson-Angus scale).**
- **Weight and metabolic parameters** (less critical vs. atypicals, but still recommended).

Clinical Pearls

- **Low dose (50–150 mg/day):** Anxiolytic/antidepressant – useful in functional disorders, dysthymia, somatic complaints.
- **Moderate dose (200–800 mg/day):** Antipsychotic – targets both positive and negative symptoms of schizophrenia.
- **Less sedation and weight gain** than many atypicals (good for patients intolerant to olanzapine/quetiapine).
- **Avoid in renal impairment** – dose adjustment mandatory if eGFR <60, contraindicated in severe renal failure.
- Often considered a "**bridge drug**" between typical and atypical antipsychotics due to its **dose-dependent profile.**

Summary:

Sulpiride is a **selective D_2/D_3 antagonist** with a **dose-dependent clinical profile**: low doses act as **antidepressant/anxiolytic**, while moderate to high doses provide **antipsychotic efficacy** with relatively less sedation, metabolic disturbance, and anticholinergic burden than other agents.

Its **unique efficacy in negative symptoms** and **functional somatic disorders** makes it especially valuable.

The main limitations are **hyperprolactinemia, dose-related EPS, and renal excretion** (requires monitoring in kidney disease).

Risperidone

℞ ***Psychodal*** *1 - 2 - 3 - 4 mg Tab*
℞ ***Psychodal*** *1 mg oral Sol^{n}.*

℞ ***Apexidone*** *0.5 - 1 - 2 - 3 - 4 mg Tab*
℞ ***Apexidone*** *1 mg oral Sol^{n}.*

Pharmacology

- **Class:** Atypical antipsychotic.
- **Mechanism of Action:**
  - **D_2 receptor antagonism** → reduces positive psychotic symptoms.
  - **5-HT_2A receptor antagonism** → improves negative/cognitive symptoms, lowers EPS risk compared with typical antipsychotics.
  - Also blocks **α_1-adrenergic, H_1-histaminic** receptors → sedation, orthostasis, weight gain.
- **Metabolism:** Hepatic via CYP2D6 → active metabolite **9-hydroxyrisperidone (paliperidone)**.
- **Half-life:** Risperidone ~3–20 h; metabolite ~20–24 h.

FDA-Approved Indications

1. **Schizophrenia** (adults, adolescents 13–17 y).
2. **Bipolar I disorder** (acute manic or mixed episodes, monotherapy or adjunct; maintenance).
3. **Irritability associated with autistic disorder** (children and adolescents 5–16 y).

Off-Label / Evidence-Supported Uses

- Behavioral disturbances in dementia (caution: ↑ mortality risk in elderly).
- Tourette's disorder and other tic disorders.
- Conduct disorder, severe aggression in children/adolescents.
- PTSD, severe anxiety disorders (adjunct, limited evidence).
- Delusional disorder.
- Borderline personality disorder (anger, impulsivity).

Dosage and Administration

1. **Schizophrenia (Adults)**
   - Initial: 1–2 mg/day (once daily or divided).
   - Titration: Increase by 1–2 mg/day every 24 h as tolerated.
   - Therapeutic range: 4–8 mg/day.
   - Maximum: 16 mg/day (rarely needed; ↑ adverse effects).

2. **Bipolar I Disorder (Mania)**
    - Monotherapy: Start 2–3 mg once daily; titrate by 1 mg/day.
    - Effective range: 2–6 mg/day.
    - Adjunct to mood stabilizer: Similar dosing, often lower needed.
3. **Irritability in Autism (5–16 y)**
    - Initial: 0.25 mg/day (<20 kg) or 0.5 mg/day (≥20 kg).
    - Titration: Adjust at ≥2-week intervals.
    - Usual effective dose: 0.5–3 mg/day (weight-based).
4. **Long-Acting Injectable (Risperdal Consta®)**
    - Typical dose: 25–50 mg IM every 2 weeks.
    - Oral overlap required for first 3 weeks.

Advantages

1. **Broad efficacy:** Effective in **positive, negative, cognitive, and affective symptoms** of schizophrenia.
2. **Multiple formulations:** Oral, ODT, solution, and **long-acting injectable** improve adherence.
3. **Lower EPS risk** than typical antipsychotics at doses ≤6 mg/day.
4. **Useful across age groups:** Only antipsychotics approved for **pediatric irritability in autism**.
5. **Relatively low cost**; available generically worldwide.
6. **Active metabolite (paliperidone)** allows continuity if switching.

Limitations & Adverse Effects

- **Extrapyramidal symptoms (EPS):** Dose-dependent; risk increases >6 mg/day.
- **Hyperprolactinemia:** Risperidone has highest risk among SGAs → galactorrhea, amenorrhea, gynecomastia, sexual dysfunction.
- **Metabolic effects:** Weight gain, dyslipidemia, hyperglycemia (less than olanzapine, more than aripiprazole/ziprasidone).
- **Sedation, dizziness, orthostatic hypotension.**
- **QT prolongation** (dose-related; caution in cardiac disease).
- **Cerebrovascular events in elderly dementia patients** → FDA boxed warning (avoid unless necessary).
- **Neuroleptic malignant syndrome, tardive dyskinesia** (long-term risk, but lower vs. first-generation antipsychotics).

Monitoring

- **Baseline and periodic:** Weight, BMI, waist circumference.
- **Metabolic profile:** Fasting glucose, HbA1c, lipids.
- **Prolactin levels** if symptoms occur.
- **Blood pressure, ECG** (if cardiac risk).
- **AIMS (Abnormal Involuntary Movement Scale)** for tardive dyskinesia monitoring.

Clinical Pearls

- Optimal dose for most patients: **2–6 mg/day**; higher doses often ↑ side effects without added benefit.
- **Prolactin elevation** is common; switch to aripiprazole or quetiapine if clinically significant.
- **LAI risperidone** improves adherence in schizophrenia and bipolar disorder; requires oral supplementation at initiation.
- In **children and adolescents**, start at very low doses and titrate slowly.
- Consider alternatives in elderly with dementia due to **stroke/mortality risk**.

Summary:

Risperidone is a **second-generation antipsychotic** with proven efficacy in **schizophrenia, bipolar mania, and autism-related irritability.**

It is widely used due to its **efficacy across symptom domains, flexible formulations (including LAI), and cost-effectiveness.**

However, clinicians must watch for **dose-related EPS, marked hyperprolactinemia, metabolic effects, and cardiovascular risks**, with careful monitoring and individualized dosing.

Aripiprazole

- ℞ ***Aripiprazole*** 1 mg Soln.
- ℞ ***Aripiprazole*** 5 -10 - 15 - 20 - 30 mg Tab
- ℞ ***Aripiprex*** 1 mg Sol$^{n.}$
- ℞ ***Aripiprex*** 10 – 15 - 20 – 30 mg Tab.
- ℞ ***Aripiprex*** 9.75 mg Vial

Pharmacology

- Second-generation (atypical) antipsychotic.
- **Mechanism of Action:**
  - **Partial agonist** at **D_2** (dopamine) and **5-HT_1A** (serotonin) receptors.
  - **Antagonist** at **5-HT_2A** receptors.

  This gives it dopamine stabilizing properties → reduces excess dopamine in mesolimbic pathways (psychosis/mania) but preserves function in neocortical pathways (mood/negative symptoms).

Therapeutic Uses of Aripiprazole

1. **Schizophrenia**
   - Effective for both positive symptoms (hallucinations, delusions) and negative symptoms (withdrawal, flat affect).
   - Preferred in first-episode psychosis because of lower metabolic burden compared to other Atypicals.
2. **Bipolar Disorder**
   - **Mania:** FDA-approved for acute manic or mixed episodes (monotherapy or adjunct).
   - **Maintenance:** Helps prevent relapse into mania; less evidence for preventing depression.
3. **Major Depressive Disorder (MDD)**
   - Used as an **adjunct to antidepressants** when response is incomplete.
   - Can accelerate response and improve energy and motivation.
4. **Irritability in Autism Spectrum Disorder (ASD)**
   - FDA-approved for children/adolescents (6–17 years).
   - Helps with aggression, tantrums, and self-injurious behavior.
5. **Tourette's Disorder**: FDA-approved for pediatric patients (6–18 years).
6. **Other Off-Label Uses** (with varying evidence)
   - Obsessive–compulsive disorder (augmentation).
   - Borderline personality disorder (anger/impulsivity).
   - Post-traumatic stress disorder (adjunct).

Dosing Guidelines

- ✓ **Schizophrenia**
  - **Adults:** Start 10–15 mg once daily.
  - Effective range: 10–30 mg/day.
- ✓ **Bipolar Disorder**
  - **Mania (adults):** Start 15 mg/day; may increase up to 30 mg/day.
  - **Pediatrics (10–17 years):** Start 2 mg/day → titrate to 10 mg/day target.
- ✓ **Major Depressive Disorder (Adjunct)**
  - Start 5 mg/day.
  - Adjust weekly in 5 mg increments.
  - Usual range: 5–15 mg/day.
- ✓ **Autism-Related Irritability**
  - Start 2 mg/day; increase gradually.
  - Effective: 5–15 mg/day depending on weight and tolerability.
- ✓ **Tourette's Disorder**
  - **<50 kg:** Start 2 mg/day; target 5–10 mg/day.
  - **≥50 kg:** Start 2–5 mg/day; target 10–20 mg/day.

Monitoring Parameters

- **Baseline & routine labs:**
  - Weight/BMI, fasting glucose, lipid profile.
  - Blood pressure.
  - CBC if history of leukopenia/neutropenia.
- **Neurologic:** Monitor for EPS, akathisia.
- **Psychiatric:** Assess suicidality (especially in depression).
- **Prolactin:** Usually decreases, but monitor if symptoms arise.

Advantages (Compared to Other Atypicals)

1. Unique **Dopamine Modulation**

   As a partial D_2 agonist, it can both reduce excessive dopamine (psychosis/mania) and boost low dopamine activity (depression, negative symptoms).

   Lower risk of hyperprolactinemia compared to risperidone or paliperidone.
2. Lower **Risk of Metabolic Syndrome**

   Less weight gain, dyslipidemia, and diabetes risk than olanzapine, quetiapine, or clozapine.

   Weight-neutral or modest weight gain in many patients.
3. Less **Sedation**

   More activating than sedating (can help in depression or negative symptoms).

   Useful when excessive drowsiness from other antipsychotics is problematic.
4. Lower **Risk of Extrapyramidal Symptoms (EPS)**

   Lower incidence of Parkinsonism, dystonia, akathisia compared to typical antipsychotics (though akathisia can still occur).
5. Prolactin-**Sparing**

   Unlike risperidone/paliperidone, it usually **reduces prolactin** (can reverse hyperprolactinemia from other agents).

Adverse Effects

- **Common:** Akathisia, restlessness, insomnia, GI upset, headache.
- **Less common:** Extrapyramidal symptoms, mild weight gain.
- **Rare but serious:**
  - Neuroleptic malignant syndrome (NMS).
  - Tardive dyskinesia (lower risk than typicals but possible).
  - Pathological gambling/impulse-control disorders (FDA warning).
  - Increased mortality in elderly with dementia-related psychosis (black box).

Contraindications / Cautions

- Hypersensitivity to aripiprazole.
- Dementia-related psychosis (black box warning).
- History of impulse-control disorders.
- Strong CYP2D6/CYP3A4 inhibitors (Fluoxetine, Paroxetine, Ketoconazole) → may require dose reduction.

Clinical Pearls

- **Akathisia is the #1 tolerability issue** → consider Propranolol or Benzodiazepines if persistent.
- Often **weight-neutral** → good for patients concerned about metabolic effects.
- **Adjunct in depression:** Start low (2–5 mg), titrate slowly to avoid activation/akathisia.
- May **improve cognition and motivation** more than sedating Atypicals.

Summary:

Aripiprazole is a versatile atypical antipsychotic with applications across psychotic, mood, and developmental disorders. Its dopamine-serotonin stabilizing mechanism provides broad efficacy with fewer metabolic and prolactin-related side effects compared to many peers. Clinicians should monitor for akathisia, insomnia, and drug interactions but can leverage its activating profile and LAI options for long-term stability.

Quetiapine

℞ ***Quitapex*** 50 mg XR Tabs.

℞ ***Quitapex*** 25-100-150-200-300-400 mg Tabs.

Pharmacological Class

- Atypical antipsychotic (second-generation antipsychotic, SGA).
- **Mechanism of action:** Antagonism at serotonin 5-HT_2A, dopamine D_2, histamine H_1, and adrenergic α_1/α_2 receptors.
- **Active metabolite (Norquetiapine):** norepinephrine transporter (NET) inhibition and 5-HT_1A partial agonism → contributes to **antidepressant and anxiolytic effects**.

Therapeutic Indications

FDA-approved

1. **Schizophrenia**
    - Adults and adolescents (13–17 years).
2. **Bipolar I disorder**
    - **Acute manic or mixed episodes** (monotherapy or adjunctive to lithium/valproate).
    - **Bipolar depression** (XR formulation; monotherapy).
    - **Maintenance treatment** (adjunctive with lithium or valproate).
3. **Major Depressive Disorder (MDD)**: Adjunctive treatment to antidepressants.

Off-label (evidence-based but not FDA-approved)

- Generalized Anxiety Disorder (GAD), particularly treatment-resistant cases.
- Insomnia (low-dose use, especially in psychiatric populations; *not recommended as routine hypnotic*).
- PTSD, agitation in dementia, or Parkinson's disease psychosis (when clozapine not tolerated).

Dosing Guidelines

A. Schizophrenia

- **Adults (IR):**
    - Day 1: 25 mg BID.
    - Titrate daily in increments of 25–50 mg BID–TID.
    - Target range: 300–800 mg/day in divided doses.

- **Adults (XR):**
    - Day 1: 300 mg once daily (evening).
    - Usual effective dose: **400–800 mg once daily**.
- **Adolescents (IR):**
    - Start 25 mg BID; titrate to 400–800 mg/day.

B. Bipolar Disorder

- **Acute mania (IR or XR, adults):**
    - Start 100 mg/day → titrate to 400–800 mg/day by day 4–7.
    - Effective dose range: **400–800 mg/day**.
- **Bipolar depression (XR, adults):**
    - Day 1: 50 mg HS → Day 2: 100 mg → Day 3: 200 mg → Day 4: 300 mg at bed time
    - **Target dose:** 300 mg at bed time (studies show no added benefit at 600 mg for bipolar depression).
- **Maintenance therapy:**
    - **300–800 mg/day**, often adjunctive with lithium or valproate.

C. Major Depressive Disorder (MDD, adjunct)

- **XR only (adults):**
    - Initial: 50 mg at bed time
    - Titrate to 150–300 mg at bed time.
    - **Effective range:** 150–300 mg/day.

Special populations

- **Hepatic impairment:** start 25 mg/day (IR) or 50 mg/day (XR); titrate slowly.
- **Renal impairment:** no formal adjustment, but monitor.

Advantages

- **Broad spectrum efficacy** across psychotic, manic, and depressive syndromes.
- **Antidepressant activity** due to Norquetiapine (unique among SGAs).
- **Lower EPS and prolactin elevation** risk compared to risperidone or typicals.
- **Sedative benefits** (useful in comorbid insomnia, agitation, or anxiety).
- **Multiple formulations** (IR vs XR) → flexible use for acute or maintenance.
- **Tolerability in Parkinson's disease/Lewy body dementia** when psychosis requires treatment (lower EPS liability).

Safety & Monitoring

- **Boxed warnings:**
    - Increased mortality in elderly with dementia-related psychosis.
    - Suicidality risk in young adults (antidepressant class warning).
- **Common adverse effects:** sedation, orthostatic hypotension, weight gain, metabolic syndrome.
- **Serious risks:** QTc prolongation, NMS, agranulocytosis (rare).
- **Monitoring:** weight, BMI, BP, fasting glucose, HbA1c, lipids, movement disorders (AIMS), ECG in high-risk patients.

Summary:

Quetiapine is a versatile atypical antipsychotic with **unique antidepressant efficacy**, relatively **low EPS risk**, and strong **sedative/anxiolytic effects**, making it a preferred choice in **bipolar depression**, **psychosis with comorbid insomnia/anxiety**, and **patients at risk of movement disorders**. The main limitations are **metabolic burden**, **sedation**, and **orthostatic hypotension**, necessitating careful dose titration and monitoring.

Olanzapine

- ℞ ***Olapex*** *5 - 10 mg Tab*
- ℞ ***Integrol*** *5- 10 mg Tab*
- ℞ ***Zyprexa*** *5- 7.5 - 10 mg Tab*
- ℞ ***Zyprexa*** *10 mg Vial.*

Pharmacology

- **Class:** Atypical antipsychotic (thienobenzodiazepine derivative).
- **Mechanism of Action:**
  - **D_2 receptor antagonist** → antipsychotic efficacy (positive symptoms).
  - **5-HT_2A antagonist** → enhances dopamine in nigrostriatal pathways, reducing EPS risk.
  - **Also binds strongly** to H_1, muscarinic (M_1–M_5), α_1-adrenergic receptors.
- **Pharmacokinetics:**
  - Half-life: ~21–54 hours (average 30 h).
  - Metabolism: Hepatic.
  - Excretion: Renal (7%) and fecal (57%).

Indications

1. **Schizophrenia (acute and chronic).**
2. **Bipolar disorder**:
   - Acute manic or mixed episodes.
   - Maintenance therapy (often with lithium or valproate).
   - Bipolar depression (in combination with fluoxetine → Symbyax®).
3. **Treatment-resistant depression (TRD):** Adjunctive (with SSRIs/SNRIs).
4. **Off-label:** Agitation in dementia (caution), borderline personality disorder (BPD), chemotherapy-induced nausea and vomiting.

Dosage and Administration

A. Schizophrenia (Adults)

- Initial: 5–10 mg once daily.
- Titration: Increase by 5 mg at intervals ≥1 week.
- Therapeutic range: 10–20 mg/day.
- Maximum: 20–30 mg/day (rare, resistant cases).

B. Bipolar Disorder

- **Acute mania/mixed episodes:** 10–20 mg/day monotherapy or adjunctive.
- **Maintenance:** 5–20 mg/day.
- **Bipolar depression (with fluoxetine):** Olanzapine 6–12 mg + fluoxetine 25–50 mg daily.

C. Depression (Adjunctive, TRD)

- 5–20 mg/day (often combined with SSRIs/SNRIs).

D. Elderly

- Start at **2.5–5 mg/day**, titrate cautiously.

Advantages

1. **High efficacy in acute psychosis and mania.**
2. **Superior efficacy in treatment-resistant schizophrenia (after clozapine).**
3. **Effective in both positive and negative symptoms.**
4. **Antimanic effect is robust** — comparable to haloperidol but with fewer EPS.
5. **Adjunctive benefit in TRD** (with fluoxetine or other antidepressants).
6. **Well tolerated in terms of EPS** due to strong 5-HT_2A antagonism.
7. **Sedative properties** useful for acute agitation, insomnia, and anxiety in psychosis.

Limitations & Adverse Effects

- **Metabolic syndrome (major drawback):**
  - Significant weight gain, hyperlipidemia, insulin resistance, risk of type 2 diabetes.
- **Sedation & somnolence:** Due to H_1 blockade.
- **Anticholinergic effects:** Dry mouth, constipation, blurred vision, cognitive impairment (esp. elderly).
- **Orthostatic hypotension:** From α_1 blockade.
- **Hyperprolactinemia:** Less than risperidone, but possible.
- **EPS:** Relatively low, but akathisia and parkinsonism may occur at higher doses.
- **Hepatotoxicity:** Mild, reversible ↑ LFTs in some patients.
- **Black Box Warning:** ↑ Mortality in elderly with dementia-related psychosis.

Monitoring

- **Baseline and periodic metabolic monitoring:** weight, BMI, waist circumference, fasting glucose, HbA1c, lipid panel.
- **Blood pressure.**
- **Liver function tests (LFTs).**

Clinical Pearls

- Among atypicals, **Olanzapine is one of the most effective** for acute mania and schizophrenia, second only to **Clozapine** in resistant cases.
- **First-line for bipolar mania** in many guidelines.
- **Combination with Fluoxetine** (Symbyax®) is uniquely approved for **bipolar depression and TRD.**
- **Not preferred long-term** due to metabolic side effects — use in younger patients with low baseline metabolic risk, or when efficacy outweighs risk.
- **LAI (Olanzapine pamoate)** is effective but requires 3-hour post-injection monitoring due to risk of **post-injection delirium/sedation syndrome (PDSS).**

Summary:

Olanzapine is a **potent atypical antipsychotic** with **broad efficacy** across schizophrenia, bipolar disorder (mania, maintenance, depression with fluoxetine), and treatment-resistant depression.

Its **major advantages** are **high efficacy, low EPS risk, strong mood-stabilizing properties, and multiple formulations**.

The **major limitations** are its **high metabolic risk, sedation, and anticholinergic effects**, which limit long-term use.

Careful **metabolic monitoring** is mandatory in clinical practice.

Amisulpride

℞ ***Amipride*** *50 - 100 - 200 - 400 mg Tab*

℞ ***Solian*** *200- 400 mg Tab*

Pharmacology

- **Class:** Atypical antipsychotic, benzamide derivative.
- **Mechanism of Action:**
  - **Selective D_2/D_3 receptor antagonist** with high limbic selectivity.
  - **No significant affinity** for muscarinic, histaminergic, adrenergic, or serotonergic receptors → reduced sedation, weight gain, and anticholinergic effects.
  - **Dose-dependent effects:**
    - **Low dose (50–300 mg/day):** Presynaptic autoreceptor blockade → ↑ dopamine release → **antidepressant, anxiolytic, pro-cognitive effects**.
    - **Moderate to high dose (400–800 mg/day):** Postsynaptic D_2 blockade → **antipsychotic effect** (positive symptoms).
    - **High dose (>800–1200 mg/day):** Striatal D_2 blockade → ↑ risk of extrapyramidal symptoms (EPS).
- **Pharmacokinetics:**
  - Oral bioavailability ~50%.
  - Excreted largely unchanged in urine (~50–60%).
  - Minimal hepatic metabolism.

Indications

- **Approved (Europe, Asia, some MENA regions):**
  - **Schizophrenia** (acute and chronic, both positive and negative symptoms).
  - **Dysthymia (persistent depressive disorder)** – at low doses (50–150 mg/day).
- Not approved in the US, but widely used in Europe.

Off-Label / Evidence-Based Uses

- Bipolar depression and mania (adjunctive).
- Treatment-resistant depression (low-dose, augmentation).
- Anxiety disorders and psychosomatic complaints.
- Negative symptoms of schizophrenia (better efficacy than typical antipsychotics).

Dosage and Administration

1. **Schizophrenia (Adults)**

- **Acute psychosis (positive symptoms):**
  - 400–800 mg/day, divided BID.
  - Maximum: 1200 mg/day.
- **Predominant negative symptoms:**
  - 50–300 mg/day, once or divided.

2. **Dysthymia / Depression (Adjunct)**

- 50–150 mg/day (commonly 100 mg/day).

3. **Elderly**

- Start at lower doses (50–100 mg/day) due to increased sensitivity and renal excretion.

Advantages

1. **Selective receptor profile:**
   - Very low risk of sedation, metabolic syndrome, or anticholinergic effects compared to olanzapine, quetiapine, and clozapine.
2. **Efficacy in negative symptoms:**
   - Clinical trials show amisulpride is superior to haloperidol and comparable to risperidone/olanzapine for negative symptoms.
3. **Low incidence of EPS** at ≤800 mg/day, due to preferential limbic vs. striatal binding.
4. **Minimal drug–drug interactions** (little hepatic metabolism).
5. **Safe in hepatic impairment** (renal excretion is the main route).
6. **Useful at low dose as antidepressant / anxiolytic**, unlike most antipsychotics.
7. **Pro-cognitive effects** observed in some studies.

Limitations & Adverse Effects

- **Hyperprolactinemia (very common):** Amenorrhea, galactorrhea, gynecomastia, sexual dysfunction.
- **Extrapyramidal symptoms (EPS):** Mainly at high doses >800 mg/day.
- **Insomnia, agitation, anxiety** (sometimes at low doses).
- **Weight gain:** Lower than atypicals (olanzapine, clozapine), but not negligible.
- **QT prolongation:** ECG monitoring advisable in at-risk patients.
- **Contraindicated in renal failure** (dose must be adjusted for renal impairment).

Monitoring

- **Renal function** (dose adjust if eGFR <60 mL/min/1.73m²).
- **ECG** (QTc prolongation risk).
- **Prolactin levels** (if symptomatic).
- **EPS assessment** (at higher doses).
- **Weight and metabolic parameters** (though lower risk than most atypicals).

Clinical Pearls

- **Unique dual profile:**
  - **Low dose = antidepressant/anxiolytic.**
  - **Moderate/high dose = antipsychotic.**
- **Excellent option for negative symptoms of schizophrenia** → especially in patients poorly responsive to other agents.
- **Preferred in hepatic disease**, but **must be avoided or reduced in renal impairment.**
- **Lower metabolic risk** → suitable for patients with obesity, diabetes, or metabolic syndrome.
- **Hyperprolactinemia** is its main drawback → long-term monitoring is essential.

Summary:

Amisulpride is a **dose-dependent atypical antipsychotic** with **proven efficacy for both positive and negative symptoms of schizophrenia**, while also offering **low-dose benefits in depression and anxiety**.
Its **advantages** include **low metabolic risk, minimal sedation, and strong efficacy in negative symptoms**.
The **main limitations** are **hyperprolactinemia, renal clearance dependence, and QT prolongation**.
It is particularly valuable when clinicians need an **antipsychotic with minimal metabolic burden** and efficacy in **negative and affective symptoms**.

Lurasidone

℞ Tudasidone 40, 80 mg Tab.
℞ Elbaluran 20, 40, 60, 80, 120 mg Tab.

Pharmacology

- Second-generation (atypical) antipsychotic in the benzothiazole class.
- It is a full antagonist at dopamine D_2 receptors and serotonin 5-HT_2A and 5-HT_7 receptors. It is a *partial agonist* at 5-HT_1A.
- It has relatively low affinity for muscarinic M1, histamine H1, and α_1-adrenergic receptors. This helps reduce side effects like sedation, orthostatic hypotension, anticholinergic effects.
- Metabolism: hepatic, mainly via CYP3A4.

Pharmacokinetics:

- Poor water solubility; must be taken with food for optimal absorption (which increases bioavailability significantly).
- Peak concentration ~1–3 hours post-dose; steady-state around 7 days.

Indications / Clinical Uses

Approved uses include:

1. Schizophrenia: Adults & adolescents (13-17 yrs.), Monotherapy
2. Bipolar I depression (major depressive episodes): Adults; children/adolescents ≥ 10 yrs in some approvals, Both monotherapy and adjunctive with lithium or valproate for adults; in younger pts monotherapy

Off-label or potential uses

1. cognitive symptoms in schizophrenia,
2. depressive symptoms,
3. agitation/psychosis in dementia (though risks are greater in that population).

Dosage & Administration

Here are typical dosing regimens, with adjustments under special conditions:

- **Schizophrenia, Adults**
    - Starting Dose ~ 40 mg once daily with food
    - Usual Range / Effective Range
    - Effective doses in trials ~ 40-160 mg/day; many effective at 40-80 mg/day.
    - **Maximum:** 160 mg/day in some adult trials; but doses >120 mg didn't clearly increase benefit vs. increased adverse effects. Many guidelines cap at ~80 mg unless special situations.

- **Schizophrenia, Adolescents (13-17 yrs.)**
  - Starting Dose ~ 40 mg once daily
  - Usual Range / Effective Range: ~ 40-80 mg/day
  - Maximum: 80 mg/day
- **Bipolar Depression, Adults**
  - Starting Dose: ~ 20 mg once daily (with food)
  - Usual Range / Effective Range: ~20-60 mg.
  - Maximum: 120 mg/day
- **Bipolar Depression, Children / Adolescents (≥ 10 yrs)**
  - Usual Range: 80 mg/day
  - Usual Range / Effective Range: Up to 80 mg/day
  - Maximum: 80 mg/day

Adjustments / Special Populations

- **Renal impairment**: Moderate/severe (creatinine clearance <50 mL/min) → start low (e.g. 20 mg/day) and cap at ~80 mg/day. Mild renal impairment often does *not* require adjustment.
- **Hepatic impairment**:
  - Mild: no dose adjustment needed.
  - Moderate: start ~20 mg/day; ceiling ~80 mg/day.
  - Severe (Child-Pugh C): max ~40 mg/day.
- **Drug interactions**:
  - Strong CYP3A4 inhibitors: *contraindicated* with lurasidone.
  - Moderate CYP3A4 inhibitors: require dosage reduction (often ~50%) and careful monitoring.
  - CYP3A4 inducers: can lower lurasidone levels; may require dosage escalation if used chronically and if efficacy is compromised.

Advantages / Benefits (Compared with other antipsychotics)

1. **Better metabolic profile**
   - Lower risk of weight gain, dyslipidemia, hyperglycemia compared to many other atypical antipsychotics (e.g. olanzapine, quetiapine, risperidone).
   - Less likely to cause sedation (due to low H1 antagonism) or anticholinergic side effects.
2. **Relatively favorable cardiovascular side-effect profile**
   - Lower risk of orthostatic hypotension given low α_1 adrenergic antagonism.
   - Minimal QTc prolongation in trials to date.

3. **Once-daily dosing**
    - Simplifies regimen and may improve adherence.
4. **Potential benefit for mood / depressive symptoms**
    - Because of its 5-HT_7 antagonism and 5-HT_1A partial-agonism it shows some antidepressant properties, which is part of the rationale for its approval in bipolar depression.

Risks / Side Effects / Monitoring

While lurasidone is generally well tolerated, there are important adverse effects and monitoring considerations:

Common / Frequent: Nausea; somnolence; akathisia; parkinsonism / extrapyramidal symptoms (EPS)

Insomnia, restlessness, anxiety also reported.

More serious but rarer risks:

- Tardive dyskinesia (as with other antipsychotics).
- Neuroleptic malignant syndrome (NMS).
- Increased risk of suicidal thoughts or behaviors in children, adolescents, young adults (as with many antidepressant/antipsychotic agents). Monitoring is required.
- Possible hyperprolactinemia (but generally lower than with some atypicals).

Monitoring:

- Regular monitoring of weight, BMI
- Fasting glucose, lipids
- ECG if risk of QT prolongation (though risk is low)
- Liver function in hepatic impairment
- Renal function in those with renal disease

Summary

Lurasidone is Atypical antipsychotic; D_2 and 5-HT_2A antagonist, 5-HT_1A partial agonist, 5-HT_7 antagonist. Indicated for Schizophrenia (adults, adolescents ≥13) & Bipolar I depression (adults; children/adolescents ≥10, monotherapy). It has Favorable metabolic profile (less weight gain, diabetes, dyslipidemia compared to other atypicals, with Minimal sedation, anticholinergic, and cardiovascular side effects. Its **Common side effects include:** Nausea, somnolence, akathisia, EPS, insomnia. Lurasidone must be taken with food for optimal absorption (which increases bioavailability significantly).

Clozapine

℞ ***Clozapex*** *25 - 100 mg Tab*

℞ ***Leponex*** *25 - 100 mg Tab*

Pharmacology

- **Class:** Atypical antipsychotic (dibenzodiazepine derivative).
- **Mechanism of Action:**
  - **Multi-receptor antagonist:**
    - **D_2 receptor:** Weak, transient blockade → low EPS.
    - **D_4 receptor:** Strong blockade (unique profile, linked to efficacy in resistant schizophrenia).
    - **5-HT_2A, 5-HT_2C antagonism:** Improves negative symptoms and cognition.
    - **H_1 histamine blockade:** Sedation, weight gain.
    - **M_1 muscarinic blockade:** Anticholinergic side effects (constipation, blurred vision).
    - **α_1-adrenergic blockade:** Orthostatic hypotension.
- **Pharmacokinetics:**
  - Half-life: 12–16 h (can extend to 24 h with chronic dosing).
  - Metabolism: Hepatic.
  - **Smoking induces CYP1A2** → lowers clozapine levels (dose adjustment required).

Indications

- **Treatment-resistant schizophrenia (TRS):** After ≥2 failed antipsychotic trials (one typically atypical).
- **Schizoaffective disorder** (resistant cases).
- **Reduction of recurrent suicidal behavior** in schizophrenia/schizoaffective disorder (unique FDA-approved indication).
- **Off-label:**
  - Parkinson's disease psychosis (low dose, 12.5–50 mg).
  - Bipolar disorder (treatment-resistant mania/depression).
  - Aggression and self-injury in severe psychiatric illness.

Dosage and Administration

- Initiation: 12.5 mg once or twice daily.
- Titration: Increase by 25–50 mg/day as tolerated.
- Therapeutic range: 300–600 mg/day (divided, usually BID).

- Maximum: 900 mg/day (rare, only if tolerated).
- Plasma levels: Target trough 350–600 ng/mL for optimal response.
- Elderly: Start at 12.5 mg/day, titrate more slowly.

Advantages

1. **Most effective antipsychotic** for treatment-resistant schizophrenia (TRS).
2. **Unique efficacy in reducing suicidality** - the only antipsychotic with FDA approval for this.
3. **Superior for negative symptoms** and cognitive improvement vs. other antipsychotics.
4. **Low risk of EPS and tardive dyskinesia**, even at high doses.
5. **Useful in Parkinson's disease psychosis** (low doses, minimal motor worsening).
6. **Possible anti-aggressive and mood-stabilizing properties.**
7. **Improved quality of life** and reduced rehospitalization in TRS patients.

Limitations & Adverse Effects

- **Agranulocytosis (0.5–1%)** → requires mandatory blood monitoring.
- **Myocarditis/cardiomyopathy (rare but life-threatening).**
- **Seizures:** Dose-dependent risk ↑ >600 mg/day.
- **Metabolic syndrome:** Severe weight gain, diabetes, dyslipidemia.
- **Sedation:** Due to H_1 blockade.
- **Constipation/ileus:** From muscarinic blockade (can be fatal if untreated).
- **Sialorrhea (excessive drooling).**
- **Orthostatic hypotension:** Risk of collapse in rapid titration.
- **Neuroleptic malignant syndrome (rare).**
- **Pneumonia:** Risk ↑ from hypersalivation + sedation (aspiration).

Monitoring

- **Hematology (mandatory):**
    - WBC and ANC monitoring required:
        - Weekly for first 6 months.
        - Every 2 weeks for next 6 months.
        - Monthly thereafter (if stable).
- **Metabolic monitoring:** Weight, BMI, glucose, HbA1c, lipids.
- **ECG & cardiac monitoring:** Baseline and periodically (risk of myocarditis, QTc prolongation).
- **Seizure risk:** Caution at high doses.

- **GI monitoring:** Constipation management is crucial.
- **Plasma drug level monitoring** if non-response or toxicity suspected.

Clinical Pearls

- **Gold standard in TRS:** Only ~30% of TRS patients respond to other antipsychotics, but 60–70% respond to clozapine.
- **Reduces all-cause mortality in schizophrenia**, largely due to suicide prevention.
- **Slow titration is mandatory** to minimize risk of hypotension, myocarditis, and seizures.
- **Smoking cessation** can ↑ clozapine levels by up to 50% (dose adjustment needed).
- **Avoid abrupt discontinuation** → risk of rebound psychosis and cholinergic rebound.
- **Best tolerated at night dosing** (major sedation and sialorrhea minimized).

Summary:

Clozapine is the **most effective antipsychotic for treatment-resistant schizophrenia and suicidality**, with unique benefits in negative symptoms, cognition, and aggression.

Its **major advantages** include unmatched efficacy, low EPS risk, and strong protective effects against suicide. The **main drawbacks** are serious risks (agranulocytosis, myocarditis, seizures, metabolic syndrome), requiring **strict blood monitoring and safety protocols**.

Despite burdensome monitoring, it remains the **gold standard for TRS** and a **life-saving drug** in psychiatry.

Modafinil

℞ ***Bravamax*** *200 mg Tab*
℞ ***Modifree*** *200 mg Tab*

Pharmacology

- **Class:**

  Wakefulness-promoting agent (eugeroic); sometimes grouped with atypical CNS stimulants.

- **Mechanism of Action:**

  Exact mechanism is not fully understood. It is believed to:

  - Increase hypothalamic histamine release.
  - Enhance dopaminergic signaling by inhibiting dopamine reuptake (DAT inhibition).
  - Affect norepinephrine, serotonin, glutamate, pathways.

  Net effect: promotes wakefulness and alertness without the pronounced sympathomimetic overstimulation seen with amphetamines.

- **Pharmacokinetics:**
  - Absorption: Well absorbed orally; peak plasma concentration in 2–4 hours.
  - Bioavailability: ~80%.
  - Distribution: ~60% protein bound (mostly to albumin).
  - Metabolism: Hepatic.
  - Half-life: 12–15 hours.
  - Elimination: Renal (as metabolites, inactive).

Psychiatric & Medical Indications

- **FDA-approved:**
  1. Narcolepsy.
  2. Obstructive sleep apnea (OSA)- related excessive daytime sleepiness.
  3. Shift work sleep disorder (SWSD).
- **Off-label / Psychiatric uses:**
  1. Adjunctive treatment in **major depressive disorder (MDD)** with residual fatigue / hypersomnia.
  2. **ADHD** (especially adults, when stimulants are not tolerated).
  3. **Cognitive dysfunction / fatigue** in schizophrenia.
  4. Fatigue in neurological conditions (e.g., multiple sclerosis, Parkinson’s disease).
  5. Augmentation in bipolar depression (cautious use).

Dosage and Administration

- **Narcolepsy / OSA:**

  200 mg once daily in the morning.
- **Shift work disorder:**

  200 mg taken ~1 hour before work shift.
- **Off-label psychiatric uses:**

  Usually 100–200 mg daily; sometimes divided doses (morning and noon).
- **Maximum studied dose:** up to 400 mg/day (no clear added benefit beyond 200 mg).

Advantages

- Compared to traditional stimulants (amphetamine, methylphenidate):
  - Lower risk of dependence and abuse (though not zero).
  - Minimal euphoria.
  - Fewer cardiovascular side effects (lower effect on heart rate and blood pressure).
  - Longer half-life allows once-daily dosing.
  - Improves wakefulness without severe jitteriness or crash.
- Useful as augmentation in depression or other psychiatric conditions with fatigue.

Adverse Effects & Limitations

- **Common adverse effects:**
  - Headache, nausea, decreased appetite, insomnia, anxiety, dry mouth.
- **Less common but serious:**
  - Stevens-Johnson syndrome (rare).
  - Severe rash / hypersensitivity.
  - Mania, psychosis, agitation (especially in vulnerable patients).
- **Limitations:**
  - Potential for misuse in academic / occupational performance enhancement.
  - Cost and availability may be restrictive.

Monitoring

- Blood pressure and heart rate (especially with cardiovascular risk).
- Psychiatric status (mood, anxiety, psychosis).
- Liver function if prolonged use / polypharmacy (due to CYP metabolism).
- Monitor for skin reactions (rash).

Clinical Pearls

- Better tolerated than amphetamines; less likely to cause rebound hypersomnia.
- Peak effect is sustained, so insomnia risk if taken late in the day.
- Adjunctive use in **treatment-resistant depression**, valuable for patients with fatigue / hypersomnia.
- CYP3A4 inducers (e.g., carbamazepine) reduce its effectiveness; inhibitors (e.g., ketoconazole) increase plasma levels.
- Can reduce efficacy of oral contraceptives via CYP3A4 induction → recommend backup contraception.

Summary

Modafinil is a wakefulness-promoting agent approved for narcolepsy, OSA-related sleepiness, and shift work disorder.

It is increasingly used off-label in psychiatry for residual depressive symptoms, ADHD, and fatigue in neurological and psychiatric disorders.

Typical dose is **200 mg/day**, with good tolerability and relatively low abuse potential compared to traditional stimulants.

Adverse effects are generally mild but require vigilance for psychiatric activation, hypertension, and rare dermatologic reactions. Its unique profile makes it a valuable option in patients needing improved alertness and daytime functioning without the drawbacks of amphetamine-like agents.

Armodafinil

℞ ***Armovigil*** *50 - 150 mg Tab*
℞ ***Wakefinate*** *50 - 150 mg Tab*

Pharmacology

- **Class:** Wakefulness-promoting agent (eugeroic); atypical stimulant.
- **Mechanism of Action:**
  - Exact mechanism not fully established.
  - Primarily acts via **dopamine transporter (DAT) inhibition**, increasing extracellular dopamine.
  - May also enhance activity in **norepinephrine, histamine, orexin/hypocretin, and glutamate pathways**, while reducing GABAergic transmission.
- **Compared to Modafinil**, Armodafinil provides **more sustained plasma concentrations** due to its stereoselective pharmacokinetics.
- **Pharmacokinetics:**
  - **Absorption:** Rapid oral absorption; Tmax ≈ 2 hours.
  - **Half-life:** ~15 hours (longer than Modafinil's ~12 h).
  - **Metabolism:** Hepatic.
  - **Excretion:** Renal (mainly as metabolites).
  - **Note:** The R-enantiomer (armodafinil) persists longer, giving smoother plasma levels and reduced late-day sleepiness compared with racemic Modafinil.

Psychiatric & Medical Indications

- **FDA-approved:**
  1. Narcolepsy.
  2. Obstructive Sleep Apnea (OSA) with residual daytime sleepiness despite CPAP.
  3. Shift Work Sleep Disorder (SWSD).
- **Off-label / Psychiatric Uses:**
  1. **Major Depressive Disorder (MDD)** – adjunctive, especially for fatigue or hypersomnia.
  2. **Bipolar Depression** – some evidence as augmentation.
  3. **ADHD** (adult patients intolerant of stimulants).
  4. **Cognitive dysfunction** in schizophrenia and neurocognitive disorders.
  5. Fatigue in neurological conditions (multiple sclerosis, Parkinson's, post-stroke).

Dosage and Administration

- **Standard Doses:**
  - Narcolepsy / OSA: 150–250 mg orally once daily in the morning.
  - Shift Work Disorder: 150 mg orally about 1 hour before shift.
- **Off-label (psychiatric augmentation):** 50–150 mg daily (morning dosing).
- **Maximum studied dose:** 250 mg/day (higher doses show no significant added benefit).

Advantages

- Compared to Modafinil:
  - Longer half-life → improved wakefulness in late afternoon/early evening.
  - less fluctuation in plasma concentration, lower risk of "wearing off."
- Compared to traditional stimulants (amphetamine, methylphenidate):
  - Lower abuse and dependence potential.
  - Minimal cardiovascular stimulation.
  - Once-daily dosing suffices for most patients.
  - Lower risk of rebound hypersomnia or "crash."

Adverse Effects & Limitations

- **Common adverse effects:**

  Headache, nausea, dry mouth, insomnia, dizziness, anxiety.
- **Less common but serious:**
  - Stevens–Johnson syndrome (rare, but serious rash risk).
  - Psychiatric symptoms: mania, hallucinations, aggression, suicidality in vulnerable individuals.
  - Cardiovascular: increased blood pressure, palpitations.
- **Limitations:**
  - Expensive relative to generics (modafinil).
  - Not curative, only symptomatic.
  - May reduce effectiveness of hormonal contraceptives (via CYP3A4 induction).

Monitoring

- **Vital signs:** Blood pressure and heart rate at baseline and periodically.
- **Psychiatric assessment:** Watch for mood instability, mania, or psychosis.
- **Dermatologic monitoring:** Report any rash immediately.

Clinical Pearls

- Morning dosing reduces insomnia risk.
- May be better suited than Modafinil for **shift workers** due to prolonged wakefulness coverage.
- In depression, armodafinil can **augment SSRIs/SNRIs** in patients with fatigue, cognitive slowing, or hypersomnia.
- Lower abuse potential makes it preferable in patients with substance-use vulnerabilities.
- Use backup contraception if patient is on hormonal birth control.

Summary

Armodafinil is a wakefulness-promoting agent approved for narcolepsy, OSA-related daytime sleepiness, and shift work disorder.

Its **longer half-life and smoother pharmacokinetic profile** provide advantages over Modafinil, particularly in maintaining alertness later in the day.

Psychiatric off-label uses include augmentation in depression, ADHD, and fatigue in various neuropsychiatric conditions. Usual dosing is **150–250 mg once daily**.

It is generally well tolerated, with mild adverse effects, lower abuse potential than traditional stimulants, and significant utility in both sleep medicine and psychiatry.

Buspirone

℞ ***Buspar*** *10 mg Tab*
℞ ***Buspalex*** *15 mg Tab*

Pharmacology

- **Class:** Anxiolytic; azaspirodecanedione derivative. Distinct from benzodiazepines, barbiturates, and other sedative-hypnotics.
- **Mechanism of Action:**
  - **Partial agonist at 5-HT1A receptors** (both presynaptic and postsynaptic).
  - **Moderate affinity for dopamine D2 receptors** (antagonist/partial agonist activity).
  - Does **not** act on GABA receptors → lacks typical benzodiazepine-like sedation, muscle relaxation, or anticonvulsant activity.
- **Pharmacokinetics:**
  - Absorption: Rapid, but significant first-pass metabolism → oral bioavailability ~4%.
  - Peak plasma: 40–90 minutes.
  - Half-life: ~2–3 hours (requires multiple daily dosing).
  - Metabolism: Hepatic, mainly via CYP3A4.
  - Elimination: Renal (metabolites).

Psychiatric Indications

- **FDA-approved:**
  - **Generalized Anxiety Disorder (GAD).**
- **Off-label Uses:**
  - Augmentation in **major depressive disorder (MDD)**.
  - Adjunct in **SSRI/SNRI-treated anxiety disorders** (e.g., panic disorder, social anxiety).
  - Management of **sexual side effects** induced by SSRIs.
  - Adjunct for **irritability and aggression** in neuropsychiatric conditions.

Dosage and Administration

- **Typical starting dose:** 7.5 mg orally twice daily.
- **Titration:** Increase by 5 mg every 2–3 days as needed.
- **Usual therapeutic range:** 20–30 mg/day, divided in 2–3 doses.
- **Maximum dose:** 60 mg/day.
- **Important:** Consistency with food or fasting is advised (food increases bioavailability).

Advantages

- **Non-sedating** (minimal psychomotor or cognitive impairment).
- **No risk of dependence, tolerance, or withdrawal**, unlike benzodiazepines.
- Safe for **long-term use**.
- Can be combined with SSRIs/SNRIs.
- Useful for patients with **substance-use disorders** or high abuse risk.
- Does not significantly potentiate alcohol or CNS depressants.

Adverse Effects & Limitations

- **Common adverse effects:** Dizziness, headache, nausea, nervousness, lightheadedness.
- **Less common:** Restlessness, blurred vision, insomnia, chest pain, tachycardia.
- **Limitations:**
    - **Delayed onset of action** (2–4 weeks), unlike benzodiazepines.
    - Ineffective for **acute anxiety or panic attacks**.
    - Short half-life → requires multiple daily dosing.
    - Efficacy may be lower in patients with previous benzodiazepine exposure (less perceived effect).

Monitoring

- No specific labs required for healthy individuals.

Clinical Pearls

- Good option for **chronic anxiety** in patients with a history of substance misuse.
- Best for **GAD**; less effective in panic disorder or phobias.
- Can be used as **SSRI augmentation** in depression or partial anxiety response.
- Because of short half-life, **TID dosing** is sometimes needed for optimal effect.

Summary

Buspirone is a **non-benzodiazepine anxiolytic** approved for **generalized anxiety disorder**, working primarily as a **5-HT1A partial agonist**. It has a **favorable safety profile**, with **no dependence or sedation**, making it suitable for long-term therapy and patients with substance-use vulnerabilities.

Onset of benefit requires several weeks, so it is **not appropriate for acute anxiety crises**. Usual doses range from **20–30 mg/day**, divided. It is most valuable as a safe, non-addictive option for chronic anxiety and as augmentation in mood and anxiety disorders.

Zaleplon

℞ ***Sleep-Aid*** 5-10 *mg Tab*

Pharmacology

- **Class:** Non-benzodiazepine hypnotic ("Z-drug"); pyrazolopyrimidine derivative.
- **Mechanism of Action:**
  - Selectively binds to the **benzodiazepine (BZ1/ω1) site** on the **GABA-A receptor complex**.
  - Enhances GABA activity → facilitates chloride influx → neuronal hyperpolarization → sedation.
  - Greater selectivity for α1 subunit of GABA-A → **sedative effects without significant anxiolytic, muscle relaxant, or anticonvulsant activity**.
- **Pharmacokinetics:**
  - **Absorption:** Rapid; Tmax ≈ 1 hour.
  - **Bioavailability:** ~30% due to extensive first-pass metabolism.
  - **Half-life:** ~1 hour (very short, compared to zolpidem or eszopiclone).
  - **Metabolism:** Primarily hepatic via **aldehyde oxidase**, minor role of CYP3A4.
  - **Excretion:** Renal (as inactive metabolites).

Psychiatric & Medical Indications

- **FDA-approved:**
  - **Short-term treatment of insomnia**, especially for **difficulty with sleep initiation** (not effective for sleep maintenance due to very short half-life).
- **Off-label / Clinical uses:**
  - Situational insomnia (e.g., jet lag, shift work).
  - Middle-of-the-night awakenings (if at least 4 hours remain for sleep).

Dosage and Administration

- **Usual adult dose:** 10 mg orally **immediately before bedtime**.
- **Range:** 5–20 mg/day.
- Elderly or hepatically impaired: 5 mg at bedtime.
- **Important notes:**
  - Take only when ready for sleep.
  - Avoid with or after heavy/high-fat meals (delays absorption).
  - Must allow at least 4 hours of sleep time after dosing.

Advantages

- **Very short half-life (~1 h):**
  - Minimal next-day residual sedation or "hangover."
  - Lower risk of psychomotor impairment compared with other hypnotics.
- **Useful for sleep-onset insomnia** and middle-of-the-night dosing.
- Less likely than benzodiazepines to cause tolerance, dependence, or withdrawal.
- No significant anxiolytic or anticonvulsant effects → narrower CNS impact.

Adverse Effects & Limitations

- **Common adverse effects:** Headache, dizziness, drowsiness, nausea, somnolence.
- **Neuropsychiatric effects:**
  Amnesia, impaired coordination, hallucinations, sleep-related behaviors (sleep-driving, sleep-eating).
- **Less common but serious:** Allergic reactions, complex sleep behaviors (FDA boxed warning for all Z-drugs).
- **Limitations:**
  - Not effective for **sleep maintenance insomnia** (due to short half-life).
  - Limited to **short-term use** (≤2–4 weeks) due to risk of dependence and tolerance.
  - Should not be combined with alcohol, opioids, or other CNS depressants.

Monitoring

- Clinical monitoring for:
  - Daytime drowsiness or next-day impairment.
  - Neuropsychiatric or abnormal sleep behaviors.
  - Potential misuse or dependence with prolonged use.
- In elderly: monitor for **falls, confusion, cognitive impairment**.

Clinical Pearls

- Best choice when **rapid sleep initiation** is the primary complaint.
- Particularly suited for **patients who wake up in the middle of the night** and still have ≥4 hours left to sleep.
- Avoid in patients with a history of **substance use disorder** or high fall risk.
- Metabolized mainly by aldehyde oxidase → fewer **CYP drug interactions** compared to zolpidem/eszopiclone.
- Should be combined with **sleep hygiene measures** for optimal benefit.

Summary

Zaleplon is a short-acting non-benzodiazepine hypnotic (Z-drug) approved for **short-term management of insomnia**, especially **sleep-onset difficulties**.

Its rapid absorption and ultra-short half-life (≈1 hour) make it ideal for patients with trouble falling asleep or those needing “middle-of-the-night” relief without next-day sedation.

Advantages include lower risk of next-day hangover and fewer CYP interactions.

Limitations are its ineffectiveness for sleep maintenance, risk of complex sleep behaviors, and need for short-term use only.

Eszopiclone

℞ ***Night Calm*** 1-3 *mg Tab*

Pharmacology

- **Class:** Non-benzodiazepine hypnotic ("Z-drug"), cyclopyrrolone derivative.
- **Mechanism of Action:**
  - Positive allosteric modulator of **GABA-A receptors** at the **benzodiazepine binding site**.
  - Unlike Zaleplon and Zolpidem, **less selective for α1 subunit** → engages α2 and α3 as well, leading to **broader hypnotic, anxiolytic, and muscle relaxant effects**.
  - Net effect: **sedation, sleep induction and maintenance**.
- **Pharmacokinetics:**
  - Absorption: Rapid; Tmax ≈ 1 hour.
  - Half-life: ~6 hours (longer than zaleplon, similar to or slightly longer than zolpidem).
  - Metabolism: Hepatic.
  - Elimination: Renal, as metabolites.

Indications

- **FDA-approved:**
  - **Treatment of insomnia**, including both **sleep onset** and **sleep maintenance**.
- **Off-label / Clinical uses:**
  - Chronic insomnia (studied for up to 6 months, making it unique among hypnotics).
  - Situational insomnia in psychiatric or medical conditions.
  - Occasionally used in circadian rhythm sleep disorders.

Dosage and Administration

- **Adults:**
  - Start at **1 mg orally immediately before bedtime**.
  - Titrate to 2–3 mg if needed and tolerated.
  - **Max dose:** 3 mg/day.
- **Elderly or hepatically impaired:**
  - Start at **1 mg**; do not exceed 2 mg.
- **Important notes:**
  - Taken only when ready to sleep.
  - Allow at least 7–8 hours for sleep before planned awakening.

Advantages

- **Effective for both sleep-onset and sleep-maintenance insomnia** due to longer half-life.
- **Approved for longer-term use (up to 6 months)** — unlike most hypnotics limited to 2–4 weeks.
- Less rebound insomnia or withdrawal compared to benzodiazepines.
- Broader GABA-A subunit activity may provide additional anxiolytic benefits.
- Generally, fewer next-day residual effects compared to long-acting benzodiazepines.

Adverse Effects & Limitations

- **Common adverse effects:**
  - Unpleasant or metallic taste (dysgeusia; occurs in ~30%).
  - Headache, dizziness, dry mouth, somnolence.
- **Serious adverse effects:**
  - Complex sleep behaviors (sleep-driving, sleep-eating) → FDA boxed warning (applies to all Z-drugs).
  - Anaphylaxis and angioedema (rare).
  - Next-day psychomotor impairment (especially with 3 mg dose).
- **Limitations:**
  - **Potential for tolerance, dependence, and misuse.**
  - Should not be combined with alcohol, opioids, or other CNS depressants.

Monitoring

- Monitor sleep patterns and effectiveness.
- Assess for next-day impairment, especially driving or hazardous tasks.
- Watch for complex sleep-related behaviors.
- In elderly: monitor for cognitive impairment, falls, or delirium.

Clinical Pearls

- Best for patients with **chronic insomnia** who need both **sleep initiation and maintenance help**.
- Dysgeusia is distinctive → if patients complain of a bitter/metallic taste, consider dose adjustment or alternative.
- Start low in elderly (1 mg) to minimize cognitive or motor side effects.
- Compared to zaleplon and zolpidem, **eszopiclone has the strongest evidence base for long-term nightly use**.
- Always combine with **sleep hygiene and CBT-I** for optimal results.

Summary

Eszopiclone is a non-benzodiazepine hypnotic used for the **short- and long-term treatment of insomnia**, effective for both sleep onset and sleep maintenance.

Usual dose is **1–3 mg at bedtime**, with 1 mg preferred in elderly.

Its advantages include evidence for up to 6 months of safe use and efficacy for sleep continuity.

Side effects include dysgeusia, next-day sedation (especially at higher doses), and rare but serious complex sleep behaviors.

It provides a good balance between efficacy and tolerability, making it a **first-line pharmacologic option for chronic insomnia** when nonpharmacologic approaches alone are insufficient.

Zopiclone

℞ ***Zopiclone 7.5*** *mg Tab*

℞ ***Hypnor 7.5*** *mg Tab*

General Information

- **Drug class:** Non-benzodiazepine hypnotic (Cyclopyrrolone derivative, "Z-drug")
- **Mechanism of action:**
  - Positive allosteric modulator of the **GABA_A receptor** (binds to benzodiazepine site, but structurally unrelated to benzodiazepines).
  - Enhances inhibitory GABAergic transmission → **sedative, hypnotic, anxiolytic, anticonvulsant, muscle relaxant** effects.

Pharmacokinetics

- Absorption: Rapid, peak plasma levels in ~1–2 hours.
- Onset of action: Within 30 minutes.
- Half-life: ~5 hours (short–intermediate acting).
- Metabolism: Hepatic (CYP3A4, CYP2E1).
- Excretion: Renal, mainly inactive metabolites.

Regulatory Status

- **Approved in Europe, Canada, Asia, Australia.**
- **Not FDA-approved in the United States** (but **eszopiclone**—the S-enantiomer of zopiclone—is FDA-approved as **Lunesta**).

Indications

Approved / Commonly Used for:

1. **Short-term treatment of insomnia**
   - Difficulty falling asleep (sleep-onset insomnia)
   - Night awakenings or poor sleep maintenance
2. **Acute or transient insomnia** (stress-related, jet lag, situational).

Dosage and Administration

Adults (oral):

- **Typical dose: 7.5 mg once nightly**, immediately before bedtime.
- **Elderly or hepatic/renal impairment: 3.75 mg nightly** (start low to minimize sedation/falls).

Duration of treatment:

- **Short-term only (2–4 weeks max, including tapering)** due to risk of dependence, tolerance, and rebound insomnia.

Advantages

- **Rapid onset and short half-life** → effective for both sleep initiation and maintenance, with reduced risk of next-day sedation compared to long-acting hypnotics.
- **Lower risk of dependence and withdrawal** vs. traditional benzodiazepines (though still present).
- **Less psychomotor and cognitive impairment** compared to diazepam or nitrazepam.
- **Generally, well tolerated** when used appropriately and short-term.
- **Alternative to benzodiazepines** in patients at risk of dependence or in elderly (when started at low dose).

Limitations / Safety Considerations

- **Risk of dependence, tolerance, and withdrawal** (especially if >4 weeks use).
- **CNS side effects:** Drowsiness, dizziness, headache, bitter/metallic taste (common adverse effect), dry mouth.
- **Complex sleep behaviors:** Sleepwalking, sleep-driving, eating while asleep (rare but serious).
- **Next-day impairment** (impaired driving, psychomotor slowing, amnesia)—dose-related.
- **Elderly:** ↑ risk of falls, fractures, confusion, delirium.
- **Drug interactions:** Potentiated by alcohol, opioids, other CNS depressants.
- **Contraindications:** Severe respiratory insufficiency, sleep apnea syndrome, myasthenia gravis, severe hepatic impairment, history of drug/alcohol abuse.

Summary:

Zopiclone is a **short-acting non-benzodiazepine hypnotic (Z-drug)** indicated for the **short-term management of insomnia**. It provides **rapid sleep induction and good sleep maintenance** with relatively **low risk of residual sedation** compared to older benzodiazepine hypnotics. Its use should remain **short-term (≤4 weeks)** due to the risks of **dependence, tolerance, and rebound insomnia**

Alprazolam

℞ ***Restolam*** 0.25- 0.5- 1 *mg Tab*

℞ ***Zolam*** 0.25- 0.5 *mg Tab*

Pharmacological Class

- Short-acting benzodiazepine.
- Mechanism: Potentiates **GABA-A receptor** activity, producing anxiolytic, sedative, hypnotic, and muscle relaxant effects.

FDA Approved Uses

1. **Generalized Anxiety Disorder (GAD)**
   Short-term management of anxiety symptoms when severe, disabling, or causing marked distress.
2. **Panic Disorder**: With or without agoraphobia.

Off-Label Uses *(not FDA-approved)*

1. **Anxiety associated with depression**
2. **Insomnia** linked to anxiety, though generally not recommended as first-line due to dependence risks.
3. **Premenstrual syndrome (PMS) / Premenstrual dysphoric disorder (PMDD)**
4. **Agoraphobia without panic disorder**, although SSRIs are generally preferred.
5. **Adjunct in chemotherapy-induced nausea and vomiting**, Esp. when related to anticipatory anxiety.
6. **Other specific phobias or situational anxiety**
   - E.g., fear of flying, performance-related anxiety (though propranolol is more common in performance anxiety).

Dosage & Administration

1. **Generalized Anxiety Disorder**
   - Initial: **0.25–0.5 mg** orally, **3 times daily**
   - Usual dose: **0.5–4 mg/day** in divided doses
   - Max: **4 mg/day** (in most guidelines)
2. **Panic Disorder**
   - Initial: **0.5 mg 3 times daily** or **0.5–1 mg at bedtime**
   - Maintenance: **2–6 mg/day** (divided, or extended-release once daily)
   - Max: **10 mg/day** (though rarely needed)

3. **Elderly / Debilitated patients**
    - Start **0.25 mg 2–3 times daily**; titrate cautiously

Advantages

- **Rapid onset of action** (within 30–60 minutes), beneficial in acute anxiety and panic attacks.
- **High efficacy** in reducing frequency and severity of panic attacks.
- Flexible formulations: IR for acute relief, XR for maintenance.
- Generally **well-tolerated short-term**, with predictable pharmacokinetics.
- Can provide **bridge therapy** while waiting for SSRIs/SNRIs to take effect in panic or anxiety disorders.

Cautions / Limitations

- **High risk of dependence and tolerance** (particularly with prolonged use).
- **Withdrawal symptoms** (rebound anxiety, insomnia, seizures if abrupt discontinuation).
- CNS depression: sedation, psychomotor impairment, cognitive effects.
- Contraindicated in patients with severe respiratory insufficiency, sleep apnea, or acute narrow-angle glaucoma.
- Metabolized by **CYP3A4** → drug interactions (e.g., with ketoconazole, erythromycin, grapefruit juice).

Summary

Alprazolam is a fast-acting benzodiazepine, highly effective for panic and acute anxiety, best used **short-term** or as adjunct therapy due to dependence risk.

Bromazepam

℞ ***Calmepam*** 1.5 - 3 *mg Tab*

℞ ***lexotanil*** 1.5 - 3 *mg Tab*

- **Drug class:** Benzodiazepine (intermediate-acting, anxiolytic)
- **Mechanism of action:** Potentiates the effect of GABA (gamma-aminobutyric acid) at GABA_A receptors → enhances inhibitory neurotransmission → anxiolytic, sedative, muscle relaxant, and anticonvulsant effects.

Pharmacokinetics

- **Absorption:** Rapid, peak plasma in 1–4 hours.
- **Half-life:** ~10–20 hours (intermediate-acting).
- **Metabolism:** Hepatic (CYP3A4); active metabolites less clinically significant than diazepam.
- **Excretion:** Renal.

FDA/EMA/WHO Regulatory Status

- **Not FDA-approved** in the United States.
- Widely prescribed in **Europe, Middle East, Asia, and Latin America**.

Indications

Approved / Commonly Used for:

1. **Anxiety disorders** (generalized anxiety, situational anxiety, adjustment disorders with anxiety).
2. **Acute anxiety symptoms** (including psychosomatic anxiety, tension, restlessness).
3. **Adjunct in depressive states with anxiety**.
4. **Short-term treatment of insomnia** related to anxiety (off-label in some regions).

Dosage and Administration

Adults (oral):

- Usual range: 1.5–3 mg 2–3 times daily.
- Moderate anxiety: 3 mg up to 3 times daily (max 9 mg/day).
- Severe anxiety (hospitalized): 6–12 mg/day, divided doses.
- Elderly/debilitated patients: Start at 1.5 mg 1–2 times daily, titrate cautiously.

Treatment duration:

- **Short-term use only (2–8 weeks, including tapering)** to avoid dependence and tolerance.

Advantages

- **Intermediate half-life**: Provides sustained anxiolytic effect without strong next-day sedation (compared to diazepam or alprazolam).
- **Rapid onset**: Effective for acute anxiety and tension states.
- **Better tolerated in some patients** compared to diazepam (less cognitive blunting, though individual response varies).
- **Flexibility of dosing**: Available in low-dose (1.5 mg) and higher-dose (3 mg, 6 mg) tablets.

Limitations / Safety Considerations

- **Risk of dependence and tolerance** (like all benzodiazepines).
- **Withdrawal symptoms** if abruptly discontinued.
- **CNS depression:** Drowsiness, fatigue, impaired coordination.
- **Drug interactions:** Enhanced sedation with alcohol, opioids, other CNS depressants.
- **Caution in elderly** (falls, confusion, delirium risk).
- **Contraindications:** Myasthenia gravis, severe respiratory insufficiency, sleep apnea, severe hepatic impairment, history of substance abuse.

Summary:

Bromazepam is an **intermediate-acting benzodiazepine** mainly used in **short-term management of anxiety disorders and acute stress-related anxiety**. It provides a balance between rapid anxiolytic relief and moderate half-life duration. However, its use should be **time-limited**, carefully dosed, and monitored due to the **risks of tolerance, dependence, and CNS depression**.

Oxazepam

℞ ***Oxepam*** 15 *mg Tab*

Pharmacology

- **Class:** Benzodiazepine; intermediate-acting anxiolytic/hypnotic.
- **Mechanism of Action:**
  - Positive allosteric modulator of **GABA-A receptors**.
  - Increases frequency of chloride channel opening → neuronal hyperpolarization → anxiolytic, sedative, hypnotic, anticonvulsant, and muscle relaxant effects.
  - Compared with some benzodiazepines, onset is relatively **slow** (not ideal for acute panic), but has a smoother profile.
- **Pharmacokinetics:**
  - Absorption: Oral, relatively slow but complete.
  - Onset: 2–3 hours.
  - Half-life: 5–15 hours (intermediate).
  - Metabolism: Direct conjugation in the liver → no active metabolites, not dependent on oxidative pathways.
  - Excretion: Renal (as glucuronides).
  - Safe in elderly and in patients with hepatic impairment because it bypasses hepatic oxidation.

Psychiatric & Medical Indications

- **FDA-approved indications:**
  - **Anxiety disorders** (including generalized anxiety, adjustment disorder with anxiety).
  - **Alcohol withdrawal syndrome** (especially for agitation, tremor, and risk of seizures).
- **Off-label / clinical uses:**
  - Short-term management of **insomnia**.
  - Anxiety associated with depression or situational stress.
  - Sometimes used in elderly as a safer benzodiazepine due to simple metabolism.

Dosage and Administration

- **Adults (Anxiety):**
  - 10–30 mg orally, 3–4 times daily.
  - Typical range: 30–120 mg/day.

- **Alcohol withdrawal:**
  - 15–30 mg orally, 3–4 times daily.
- **Elderly or debilitated patients:**
  - Lower initial dose (10 mg, 2–3 times daily).

Advantages

- **Metabolism by direct glucuronidation:**
  - Ideal for elderly patients.
  - Safer in patients with **hepatic impairment or liver disease** (e.g., cirrhosis, hepatitis).
- **Intermediate half-life:**
  - Less risk of daytime sedation than long-acting benzodiazepines.
  - Less rebound anxiety than very short-acting ones.
- **Useful in alcohol withdrawal** (especially in liver-diseased patients where Diazepam/Chlordiazepoxide are contraindicated).
- Lower risk of drug accumulation and oversedation.

Adverse Effects & Limitations

- **Common adverse effects:**
  - Sedation, drowsiness, fatigue, dizziness, impaired coordination.
  - Cognitive and psychomotor slowing.
- **Serious adverse effects:**
  - Dependence, tolerance, withdrawal (with prolonged use).
  - Respiratory depression (especially with other CNS depressants).
  - Paradoxical reactions (agitation, aggression, disinhibition).
- **Limitations:**
  - **Not rapid-onset** → less useful for acute panic attacks.
  - Short-term use only (risk of dependence).
  - Requires multiple daily dosing due to intermediate half-life.

Monitoring

- Monitor for:
  - **Signs of misuse or dependence**.
  - **Sedation, falls, or cognitive impairment**, particularly in elderly.
  - Drug interactions with other CNS depressants (opioids, alcohol, antihistamines).

Clinical Pearls

- Preferred benzodiazepine in **elderly and patients with liver disease** due to direct conjugation metabolism.
- Effective and safe option in **alcohol withdrawal with hepatic impairment**.
- Not the first choice for acute anxiety relief because of slower onset.
- Useful for patients requiring **steady anxiolysis without strong sedation**.
- Tolerance develops more slowly compared to some shorter-acting benzodiazepines.

Summary

Oxazepam is an intermediate-acting benzodiazepine indicated for **anxiety disorders** and **alcohol withdrawal syndrome**. Its unique advantage is metabolism via **glucuronidation**, making it particularly suitable for **elderly patients and those with hepatic impairment**. Usual dosing is **10–30 mg up to 3–4 times daily**. It is less effective for acute panic due to its slower onset but provides steady anxiolysis with reduced risk of accumulation. While generally safe, it shares class risks of sedation, dependence, and cognitive impairment, limiting its use to **short-term therapy and carefully selected patients**.

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This is a short and goal-directed book discussing psychotropic medications. Instead of diving into theoretical details, it focuses on what truly matters: how psychiatric medications are used, why they are prescribed, and how to apply them safely and effectively.

Each section is designed with the busy professional in mind, organized to allow quick access to key information, with emphasis on indications, dosage, advantages, and practical considerations.

Our goal is to bridge the gap between theory and practice. Whether you are a psychiatry trainee, a practicing clinician, or a student seeking clarity, this guide will help you navigate psychiatric drug treatment with confidence.